ACCP Updates in Therapeutics®
2015: Critical Care Pharmacy
Preparatory Review Course

Cardiovascular Critical Care

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Learning Objectives

1. Describe cardiovascular anatomy, inherent physiologic function, and circulation in relation to hemodynamic assessment.
2. Evaluate patients and devise a treatment strategy for patients with cardiogenic shock, considering pharmacodynamic response to vasopressors/inotropes.
3. Identify cardiovascular disease states associated with cardiogenic shock.
4. Understand the fundamentals in management of cardiovascular diseases in critically ill patients.
5. Recognize the options for and roles of mechanical circulatory support and heart transplantation as advanced therapies for heart failure and/or cardiogenic shock.

Abbreviations in This Chapter

ABG	Arterial blood gas
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome(s)
ACT	
AF	Atrial fibrillation
ARB	Angiotensin receptor blocker
AV	Atrioventricular
BNP	Brain natriuretic peptide
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CHADS$_2$	Congestive heart failure, hypertension, age older than 75, diabetes, and prior stroke or transient ischemic attack
CVP	Central venous pressure
ECHO	Echocardiography
ECMO	Extracorporeal membrane oxygenation
HIT	Heparin-induced thrombocytopenia
HOCM	Hypertrophic obstructive cardiomyopathy
ICU	Intensive care unit
LV	Left ventricle/ventricular
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
MAP	Mean arterial pressure
MCS	Mechanical circulatory support
MI	Myocardial infarction
NSTEMI	Non–ST-segment elevation myocardial infarction
OLH	Outlying hospital

PCI	Percutaneous coronary intervention
PVR	Pulmonary vascular resistance
RV	Right ventricle/ventricular
SA	Sinoatrial
STEMI	ST-segment elevation myocardial infarction
SVR	Systemic vascular resistance
VAD	Ventricular assist device
VT	Ventricular tachycardia

Self-Assessment Questions
Answers and explanations to these questions may be found at the end of this chapter.

Questions 1–8 pertain to the following case.
A 58-year-old man (height 71 inches, weight 106 kg) was transferred to the intensive care unit (ICU) from an outlying hospital (OLH) after 24 hours of progressively worsening chest pain and shortness of breath. He arrives on 6 L of oxygen by high-flow nasal cannula, with a heparin infusion at 16 units/kg/hour and dopamine infusing at 15 mcg/kg/minute by peripheral line. Notes show that he was bradycardic (heart rate [HR] ranging from 50 to 58 beats/minute) and hypotensive (78/49 to 86/55 mm Hg) on presentation to the OLH. His 12-lead electrocardiogram (ECG) at the OLH showed ST-segment depression in leads V2 and V3. Given his chest pain and ECG findings, aspirin 324 mg (chewed and swallowed), clopidogrel 600 mg, and morphine 4 mg intravenously once were administered before transfer. Notes also show that β-blockers and nitroglycerin were held because of bradycardia and hypotension.

His medical history is significant for medical nonadherence, hypertension, diabetes, hyperlipidemia, and heart failure with preserved ejection fraction (HF*p*EF), with a last-reported left ventricular ejection fraction (LVEF) of 65% 1 year ago.

- Vital signs on transfer: BP 87/52 mm Hg, HR 85 beats/minute, respiratory rate 19 breaths/minute, temperature 37.6°C
- The team's assessment indicates ongoing distress, radiating chest pain 7 of 10, evidence of rales, absence of any cardiac murmurs, and presence of a right radial arterial line.

- A preexisting urinary catheter with 20 mL of urine in the reservoir is also present (the patient reports that his last void was yesterday morning). According to OLH records, only 30 mL of urine was reported before time of transfer.
- His chest radiography reveals evidence of diffuse patchy opacities; however, the report indicates that an infiltrate cannot be ruled out.
- His serum chemistry panel results are as follows: sodium 132 mEq/L, potassium 4.2 mEq/L, chloride 102 mEq/L, carbon dioxide 22 mEq/L, blood urea nitrogen (BUN) 34 mg/dL, serum creatinine (SCr) 1.9 mg/dL, and glucose 163 mg/dL.
- Results of the complete blood cell count (CBC) are as follows: white blood cell count (WBC) 11.3×10^3 cells/mm^3, hemoglobin 10.9 g/dL, hematocrit 31.1%, and platelet count 213,000/mm^3.
- Additional laboratory values include troponin 3.9 ng/mL, aspartate aminotransferase (AST) 14 IU/L, alanine aminotransferase (ALT) 46 IU/L, hemoglobin A1C (A1C) 8.3%, and brain natriuretic peptide (BNP) of 1423 pg/mL.

1. Which is the most likely cause of this patient's admission and transfer?

   A. Septic shock caused by suspected pneumonia with subsequent myocardial depression and demand ischemia.
   B. Cardiogenic shock caused by acute on chronic decompensated systolic heart failure.
   C. Cardiogenic shock caused by a suspected posterior ST-segment elevation myocardial infarction (STEMI).
   D. Cardiogenic shock caused by a suspected non–ST-segment elevation myocardial infarction (NSTEMI) affecting the lateral wall.

2. Given this patient's presentation, which coronary artery is most suggestive of a culprit lesion?

   A. Left main coronary artery.
   B. Left anterior descending artery.
   C. Left circumflex coronary artery.
   D. Right coronary artery.

3. The interventional cardiologist who is evaluating the patient for potential revascularization asks the ICU team to place a central venous catheter. Which changes/interventions regarding this patient's hemodynamic support would be best to recommend?

   A. Increase dopamine to achieve a mean arterial pressure (MAP) greater than 65 mm Hg.
   B. Convert the patient to norepinephrine, and titrate the dose to achieve a MAP greater than 65 mm Hg while weaning off dopamine.
   C. Initiate milrinone at 0.375 mcg/kg/minute, and continue dopamine at 15 mcg/kg/minute.
   D. Administer 1000 mL of normal saline as a bolus because of low urine output.

4. The patient has been taken to the cardiac catheterization laboratory, and a "code blue" is called overhead for immediate emergency response to this patient's procedural area. On arrival, chest compressions have just been paused for defibrillation, and a single dose of epinephrine has been administered. The interventional team indicates that, when attempting visualization of the right coronary artery, the patient went into ventricular tachycardia (VT). The patient's telemetry monitor now shows a sinus tachycardia with noted ectopy—HR of 113 beats/minute and blood pressure (BP) of 84/52 mm Hg. The cardiologist asks for recommendations for an antiarrhythmic because he is concerned about a VT relapse, given the bigeminy revealed on telemetry. Which agent would be best to recommend?

   A. Lidocaine 100 mg intravenous push over 2–3 minutes, followed by an infusion at 1 mg/minute.
   B. Amiodarone 300 mg intravenous push over less than 1 minute.
   C. Metoprolol 10 mg intravenous push over 1–2 minutes.
   D. Diltiazem 20 mg intravenous push over 2 minutes, followed by a continuous infusion at 5 mg/hour and titrated to maintain a HR less than 110 beats/minute.

5. The patient returns to the ICU after his left heart catheterization, which was performed through the femoral artery. In addition to his acute decompensation, which major procedural complication is of greatest concern during the next 12 hours?

   A. Bleeding (particularly retroperitoneal bleeding).
   B. Dissection/rupture.
   C. Stent thrombosis.
   D. Papillary muscle rupture.

6. The patient is currently on dopamine at 12 mcg/kg/minute and norepinephrine at 0.08 mcg/kg/minute with an HR of 108 beats/minute, a BP of 82/51 mm Hg, a cardiac index of 2.0, a central venous pressure (CVP) of 26 mm Hg, and a pulmonary artery pressure of 29/21 mm Hg. The physician would like to augment management of this patient's hypotension but asks for your recommendation out of concern for the patient's right ventricular (RV) function, as evidenced by the rising CVP despite only mildly elevated pulmonary artery pressures. Moreover, the physician's goal is to wean the dopamine while increasing the patient's systemic vascular resistance (SVR) without affecting the pulmonary vascular resistance (PVR) much, if at all. Which strategy would be best to recommend?

   A. Keep the current infusions and reevaluate later.
   B. Initiate phenylephrine at 1 mcg/kg/minute and wean the dopamine off if MAP is greater than 65 mm Hg.
   C. Initiate vasopressin at 0.04 unit/minute and wean the dopamine off if MAP is greater than 65 mm Hg.
   D. Administer a 1-L bolus of normal saline and wean the dopamine off if MAP is greater than 65 mm Hg.

7. Hours later, this patient goes into atrial fibrillation (AF) with an HR of 126 beats/minute; however, the patient's BP remains 86/56 mm Hg according to the regimen selected in the previous question. Which agent would you most likely administer to manage the patient's AF?

   A. Amiodarone 150 mg intravenous push, followed by a continuous infusion at 1 mg/minute.
   B. Amiodarone 150 mg intravenous infusion over 10 minutes, followed by a continuous infusion at 1 mg/minute.
   C. Metoprolol 5 mg intravenous push once, followed by 5 mg intravenous push every 6 hours.
   D. Diltiazem 20 mg intravenous push, followed by a continuous infusion at 5 mg/hour and titrated to maintain an HR of less than 110 beats/minute.

8. If this patient did have a myocardial infarction (MI) during his stay (regardless of intervention or medical management) with an LVEF greater than 40%, which most accurately depicts the medication-related quality metric that would not require initiation or documentation of contraindications at this time?

   A. $P2Y_{12}$ contraindication.
   B. Statin contraindication.
   C. β-Blocker contraindication.
   D. Angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor antagonist (ARB) contraindication

I. **CARDIOVASCULAR FUNDAMENTALS OVERVIEW**

A. The myocardium has five functions and distinctive properties:
1. *Chronotropy*: Ability to generate an electrical impulse at an intrinsic rate
2. *Dromotropy*: The speed and ability to facilitate electrical impulse conduction
3. *Inotropy*: Ability to contract in relation to a given preload, afterload, and HR
4. *Bathmotropy*: Demonstration of an intrinsic excitatory threshold
5. *Lusitropy*: Relaxation of the myocardium, independent from termination of contraction
6. Other related terms:
   a. *Preload*: Volume of blood (represented in most cases by a pressure) in a *ventricular cavity* at the end of diastole immediately before contraction, imparting stretch on a resting myocardial sarcomere
   b. *Afterload*: The pressure that a *ventricle* must overcome to generate cardiac output. The greater the afterload (vascular resistance or impedance), the greater the amount of energy and force required to enable ejection of blood from a ventricle and vice versa

B. Coronary Artery Circulation
1. Myocardial perfusion occurs through the coronary arteries during diastole.
2. Coronary artery anatomy and perfusion are not the same in everyone.
3. ECG defects, hemodynamic assessment, and patient symptoms may assist with coronary artery disease (CAD) localization.
4. Circulatory dominance:
   a. Right dominant: Posterior descending artery and atrioventricular (AV) nodal artery arise from the right coronary artery (85% of the population).
   b. Left dominant: Posterior descending artery arises from the circumflex artery (8% of the population).
   c. Codominant: Posterior descending artery arises from branches of the circumflex and the right coronary artery (7% of the population).
   d. Other notable variations: The sinoatrial (SA) node may have variation in the vessels that supply it; it is most commonly perfused by the right coronary artery (about 70%), circumflex (about 25%), and right coronary artery and circumflex (about 5%).
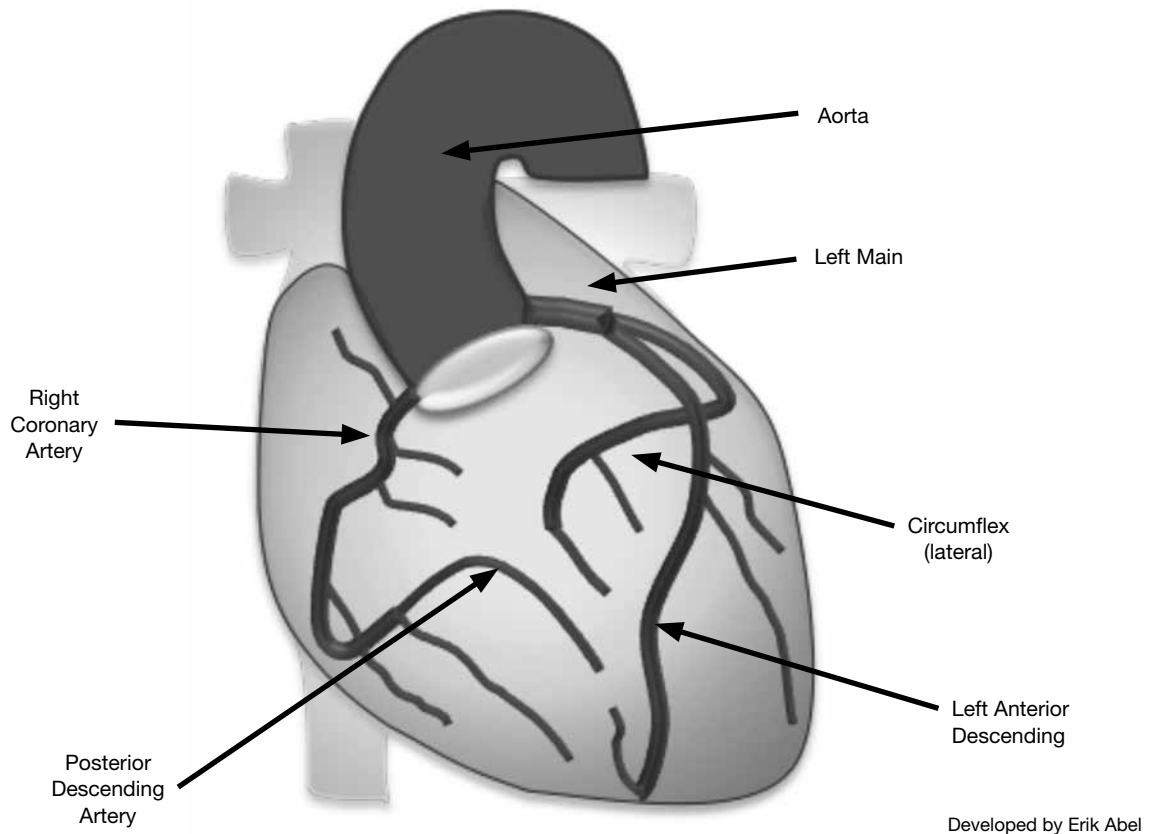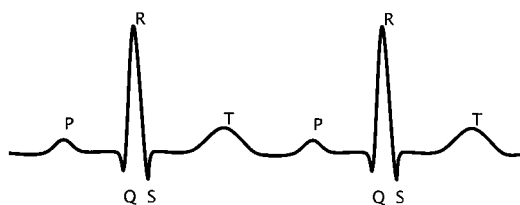
Figure 1. Coronary artery circulation.

 C. Anatomy in Relation to the ECG
  1. A single lead of an ECG tracing is a summative representation of the action potentials occurring from a single cell, facilitating myocardial conduction, contraction, and relaxation.
  2. A 12-lead ECG can provide a geographic representation of conduction within the myocardial tissue. Conduction abnormalities within specified leads may indicate perfusion defects in some clinical scenarios (i.e., acute coronary syndromes [ACS]).

Action Potential
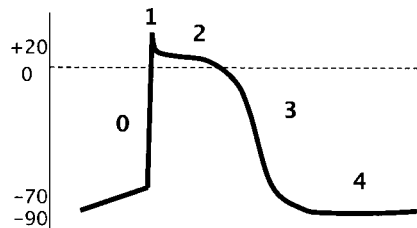
Phase	Electrolyte movement	Conduction change
0	Na+ influx into cell	Depolarization
1	Rrefractory Ca^{2+} and Cl^- into cell	Effective Refractory Period
2	Ca^{2+} into cell and K^+ out of cell	
3	K+ out of cell	Repolarization
4	Resting Membrane Potential	

Electrocardiogram (ECG)

ECG point	Representation
P	Sinoatrial (SA) node impulse generation
PR interval	Duration for conduction to occur from the SA node through the AV node, bundle of His, bundle branches and Purkinje fibers
QRS	Concurrent atrial repolarization and ventricular depolarization
ST segment	Ventricular refractory period
T	Ventricular repolarization
QT interval	Duration for atrial and ventricular repolarization
RR interval	Duration between ventricular depolarizations (represents heart rate)
U	No listed or commonly visualized; may be more prominent in hypothermia or in severe electrolyte depletions

12 — Lead Electrocardiogram (ECG)

Limb leads				Precordial Leads			
I	Anterolateral (Circumflex)	aVR		V1	Anteroseptal (LAD)	V4	Anteroapical (Distal LAD)
II	Inferior (RCA)	aVL	Anterolateral (Circumflex)	V2	Anteroseptal (LAD) Posterior (RCA)	V5	Anterolateral (Circumflex)
III	Inferior (RCA)	aVF	Inferior (RCA)	V3	Anteroapical (Distal LAD) Posterior (RCA)	V6	Anterolateral (Circumflex)

adapted from ACLS instructor book

Figure 2. Anatomy in relation to the ECG.


II.   HEMODYNAMIC MANAGEMENT AND THE HEART

A.   Hemodynamic Assessment Relies on the Clinician's Clinical Interpretation to:
1.   Understand cardiovascular circulation (Figure 3) and pathophysiology contributing to the hemodynamic parameters in isolation and in the context of other hemodynamic parameters
2.   Account for trends in the values in light of end-organ function and surrogates of oxygen delivery, and use VO_2 mismatch
3.   Understand the roles of hemodynamic tools, limitations in use, and interpretation of the devices/ technology.
4.   Identify appropriate therapeutic targets (Figure 4), and apply the pharmacologic/pharmacodynamic principles (Table 1) to initiate, modify, or discontinue therapy depending on clinical response

B.   Advantages and Disadvantages of Invasive Hemodynamic Monitoring for Assessing Cardiac Output and/or Volume Status
1.   Hemodynamic monitoring techniques facilitate diagnosis, but they should not be mistaken for therapeutic interventions.
2.   Very little evidence has shown improved outcomes with advanced hemodynamic monitoring of any type, likely because patient management is dependent on clinician interpretation and reaction.
3.   Diligent use and skilled interpretation of these technologies, together with patient assessment, can be used to guide therapeutic interventions.
4.   See comparisons of invasive and minimally invasive hemodynamic monitoring devices (see table 2 in the Shock and Resuscitation chapter).

C. Pharmacologic Support in Cardiovascular Critical Illness (see Table 1 and "Shock Syndromes" for hemodynamic basic principles)

RA = Right Atrium
RV = Right Ventricle
TV = Tricuspid Valve
PV = Pulmonic Valve

At End of Diastole (Filling)
CVP ≈ RAP ≈ PAD ≈ PAOP ≈ LAP ≈ LVEDP

Left Atrium = LA
Left Ventricle = LV
Mitral Valve = MV
Aortic Valve = AV
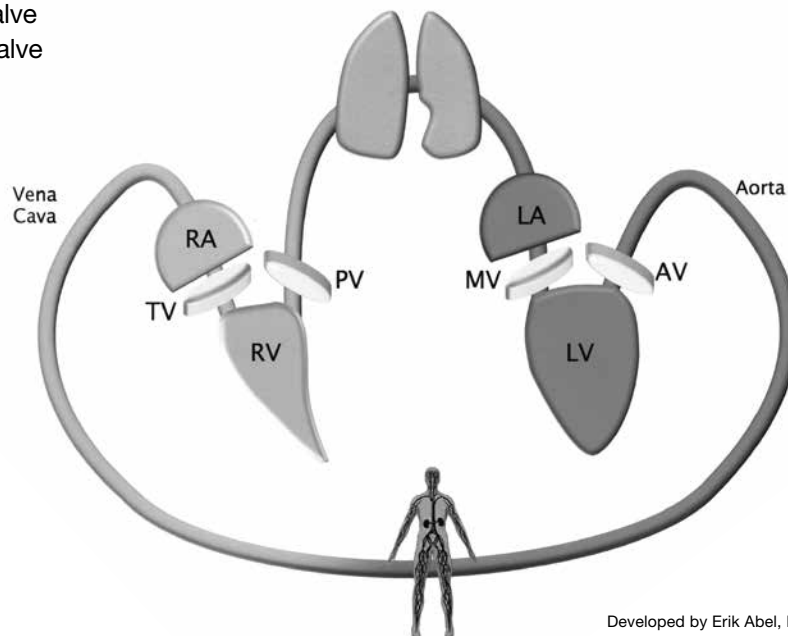
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Figure 3. Cardiovascular systemic circulation.
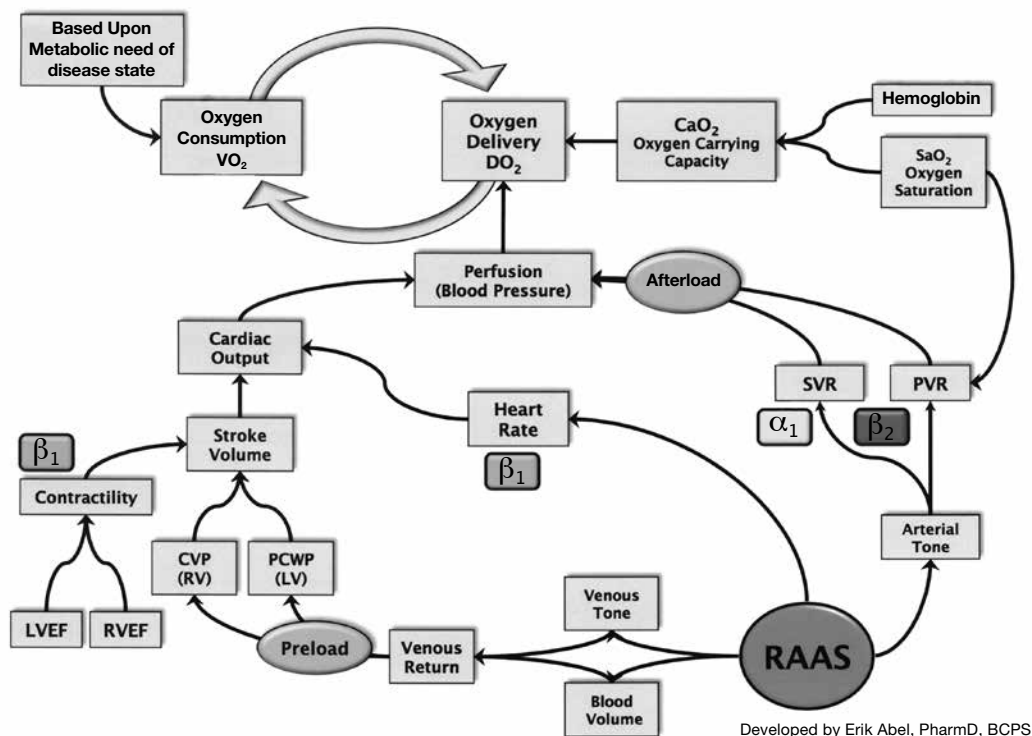
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Figure 4. Integrated model of the hemodynamic parameters and therapeutic targets.

Table 1. Pharmacologic Support in Cardiovascular Critical Illness (Br J Pharmacol 2012;165:2015-33; J Am Coll Cardiol 2014;63:2069-78; 2011;xiv, 461 p.; Circulation 2008;118:1047-56; 2014;xix, 1490 p.; J Pharm Pract 2011;24:44-60)

Vasopressors	Dopa	α_1	β_1	β_2	Other Mechanism	HR	CVP	CO	SVR	PVR
Dopamine[a]	+++++	+++	++++	++		↑	↔	↑	↔ or ↑	↔ or ↑
Epinephrine[a]		++++	++++	+++		↑	↔	↑	↑	↑
Norepinephrine[a]		+++++	+++	++		↑	↔	↑	↑	↑
Phenylephrine		+++++				↔ or ↓	↔	↑	↑	↑
Vasopressin	N/A				V_1 and V_2 agonism	↔ or ↓	↔	↔ or ↓	↑	↔ or ↓
Inotropes										
Dobutamine		+	++++	++		↑	↔	↑	↔ or ↓	↔ or ↓
Isoproterenol			+++++	+++++		↑	↔	↑	↔ or ↓	↔ or ↓
Milrinone[b]	N/A				PDE_3 inhibition	↔ or ↑	↔	↑	↓	↓
Vasodilators										
Nitroglycerin					cGMP	↔ or ↑	↔ or ↓	↔ or ↑	↔ or ↓	↔ or ↓
Nitroprusside					cGMP	↔ or ↑	↔ or ↓	↔ or ↑	↔ or ↓	↓
Nesiritide					cAMP	↔ or ↑	↔ or ↓	↔ or ↑	↓	↓
Nitric oxide (inhaled)					cGMP	NA	↔	↔ or ↑	↔	↓
Epoprostenol (inhaled)					cAMP	N/A	↔	↔ or ↑	↔	↓

[a]High doses associated with increasing α1 activity.

[b]Normal half-life is 2.5 hours but is eliminated renally. Loading dose rarely used in routine management.

CVP = central venous pressure; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; N/A = not applicable; PDE3 = phosphodiesterase type 3; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance.

III. CARDIOGENIC SHOCK

    A.   Characterized by Three Hallmark Attributes:
        1.   Sustained hypotension unresponsive to fluid administration alone (SBP less than 90 mm Hg for at least 60 minutes)
        2.   Evidence of myocardial dysfunction with reduced cardiac index (less than 2.2 L/minute/m^2)
        3.   Signs and symptoms of malperfusion in the setting of elevated cardiac filling pressures (e.g., pulmonary capillary wedge pressure [PCWP] greater than 18 mm Hg)

    B.   Signs and Symptoms: See Heart Failure section.

    C.   Epidemiology: Without appropriate diagnosis and management, in-hospital mortality rates as high as 60% have been described Semin Respir Crit Care Med 2011;32:598-606.
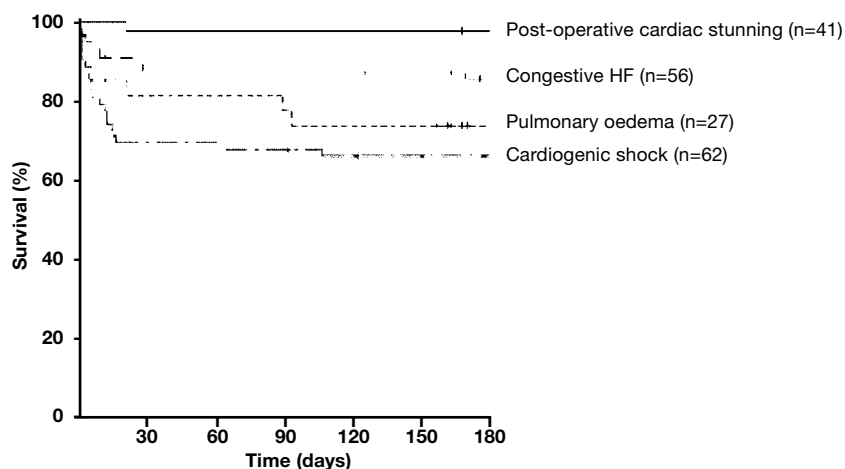
Figure 5. Survival rates of ICU patients over time presenting with different acute heart failure syndromes (Crit Care 2010;14:201).

D. Etiology
    1. Usually caused by left ventricular (LV) failure secondary to an acute MI, but a list of other potential causes can be found in Box 1
    2. May be multifactorial, including one or more of the causative etiologies; however, can also coexist with other types of shock syndromes

Box 1. Potential Causes of Cardiogenic Shock (2014;xix, 1490 p.; Semin Respir Crit Care Med 2011;32:598-606; Cardiol Clin 2013;31:567-80, viii; Cardiol Clin 2013;31:519-31, vii-viii)

Left Ventricular Failure
- Large MI
- Small MI with preexisting systolic heart failure
- Reinfarction
- Septic shock with severe myocardial depression

RV Failure
- RV infarction
- End-stage pulmonary hypertension

Acute Mechanical Dysfunction
- Papillary muscle rupture or chordal rupture with subsequent severe mitral regurgitation
- Free-wall rupture
- Ventricular septal rupture
- Cardiac tamponade

Cardiomyopathy
- End-stage heart failure
- Myocarditis
- Peripartum cardiomyopathy
- Left ventricular outflow tract obstruction
- Stress-induced cardiomyopathy (i.e., takotsubo)

Box 1. Potential Causes of Cardiogenic Shock *(continued)*
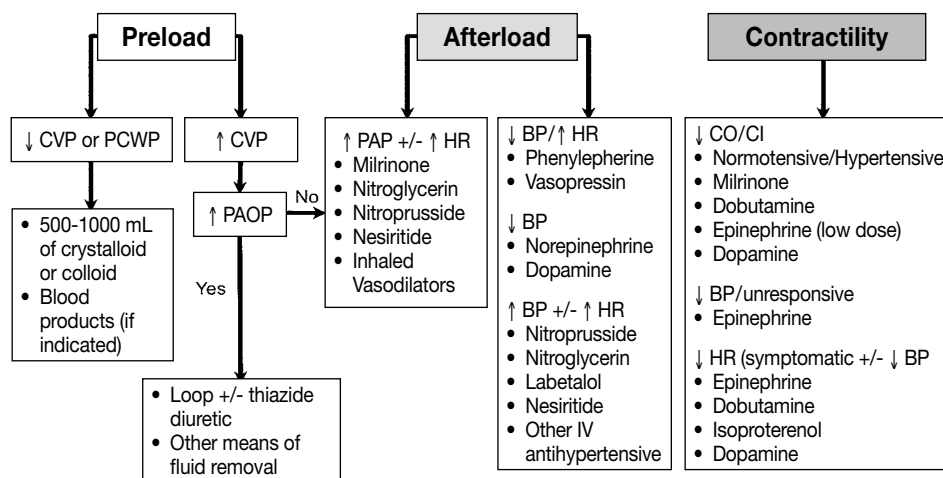

Valvular Disease
- Acute aortic regurgitation
- Ischemic mitral regurgitation
- Aortic or mitral stenosis with tachyarrhythmia or other condition causing decompensation
- Infectious endocarditis
- Prosthetic valve dysfunction or thrombosis

Arrhythmia

Other Conditions
- Prolonged cardiopulmonary bypass and/or coronary air embolus
- Cardiac trauma (blunt or penetrating)
- Heart transplant rejection
- Pulmonary embolism
- Medical nonadherence

E. Resuscitation/Treatment
  1. Treatment largely depends on managing underlying chronic or acute cardiovascular disease(s) outlined in Box 1, with consideration given to chronicity of clinical changes before onset of shock.
  2. Means of management will be primarily discussed under the Major Contributing Etiologies heading in sections III–VI.
  3. Hemodynamic management and pharmacotherapeutic considerations
     a. Because cardiogenic shock may have different underlying, contributing etiologies, hemodynamic management requires careful interpretation of clinical values. Treatment strategies could be devised according to the algorithm in Figure 6.
     b. Sepsis Occurrence in Acutely Ill Patients (SOAP) II landmark trial (N Engl J Med 2010;362:779-89)
        i. International multicenter trial (n=1679) that compared the 28-day mortality of norepinephrine with that of dopamine in the management of shock
           (a) Included if signs of malperfusion and MAP less than 70 mm Hg or SBP less than 100 mm Hg, despite adequate fluid challenge (at least 1000 mL of crystalloids or 500 mL of colloids unless the CVP was greater than 12 mm Hg or the pulmonary artery occlusion pressure was greater than 14)
           (b) Allowed titration to maximums of norepinephrine 0.19 mcg/kg/minute versus dopamine 20 mcg/kg/minute, after which open-label norepinephrine was allowed (open-label norepinephrine doses did not exceed 1.1 mcg/kg/minute during the study period)
           (c) Epinephrine and vasopressin were permitted as rescue agents (similar use in both groups).
           (d) Dobutamine use was greater in the norepinephrine group (19.4% vs. 14.8%).
        ii. Showed that dopamine was associated with a significantly higher mortality rate than was norepinephrine with or without dobutamine in patients with cardiogenic shock in subgroup analysis
        iii. Specifically, dopamine was associated with more adverse events than norepinephrine in the management of all shock subtypes, predominantly driven by the incidence of arrhythmias (24.1% vs. 12.1%, p<0.001). Tachyarrhythmias with dopamine had the greatest incidence within the first 36 hours after randomization.

Preload		Afterload		Contractility

↓ CVP or PCWP | **↑ CVP**

↑ PAP +/- ↑ HR
- Milrinone
- Nitroglycerin
- Nitroprusside
- Nesiritide
- Inhaled Vasodilators

↓ BP/↑ HR
- Phenylepherine
- Vasopressin

↓ BP
- Norepinephrine
- Dopamine

↑ BP +/- ↑ HR
- Nitroprusside
- Nitroglycerin
- Labetalol
- Nesiritide
- Other IV antihypertensive

↓ CO/CI
- Normotensive/Hypertensive
- Milrinone
- Dobutamine
- Epinephrine (low dose)
- Dopamine

↓ BP/unresponsive
- Epinephrine

↓ HR (symptomatic +/- ↓ BP
- Epinephrine
- Dobutamine
- Isoproterenol
- Dopamine

↑ PAOP — No — Yes

- 500-1000 mL of crystalloid or colloid
- Blood products (if indicated)

- Loop +/- thiazide diuretic
- Other means of fluid removal

Adapted from: Blais, DM. PSAP- IV: Critical and urgent care. 2010

Figure 6. Shock management and treatment considerations based on hemodynamic indices.

Patient Cases

Questions 1–6 and Question 8 pertain to the following case.

J.M. is a 58-year-old man with a history of CAD, type 2 diabetes mellitus, hyperlipidemia, gastroesophageal reflux disease, hypertension, obstructive sleep apnea, and ischemic cardiomyopathy after a STEMI 2 years ago left him with two drug-eluting stents in his proximal and mid-left anterior descending artery. Records indicate an LVEF of 30–35% and moderate mitral regurgitation from 6 months ago. He is admitted to the cardiac care unit for severe shortness of breath and altered mental status, where he is currently on CPAP (continuous positive airway pressure). He has gained 13 kg during the past 2 weeks (now weighs 121 kg) and has had decreased urine output, despite having had his diuretic dose increased. Home medications include the following: aspirin 81 mg once daily, ticagrelor 90 mg every 12 hours, pantoprazole 40 mg once daily, metoprolol tartrate 25 mg every 12 hours, atorvastatin 40 mg once daily, insulin glargine 10 units every night, metformin 500 every 12 hours, furosemide 40 mg twice daily, and potassium chloride 20 mEq twice daily. His wife states that he was taking clopidogrel until 1 month ago but could not afford it, so his primary care physician provided ticagrelor samples. A physical examination reveals rales throughout his lung fields. He is afebrile, anxious, and alert.

1. Given J.M.'s comorbidities, some drugs or drug classes have proven mortality benefits. Which group of added or modified medications, not on the patient's home medication profile, might best have helped slow the progression of his disease and confer mortality benefits?

   A. Amlodipine, clopidogrel, and sitagliptin.
   B. Spironolactone, lisinopril, and carvedilol.
   C. Pravastatin, amlodipine, and aspirin 325 mg.
   D. Prasugrel, sildenafil, and atenolol.

Patient Cases (*continued*)

2. Given the patient's presentation, which group of diagnostic tests would be most helpful to guide your recommendations to the team for J.M.'s current management? (Assume that a basic metabolic panel [Chem 7], a pulse oximetry, and a capillary blood glucose have already been completed.)

    A. Urine culture, respiratory culture, lactate and procalcitonin.
    B. Chest radiography, arterial blood gas (ABG), liver function tests, and serial troponins.
    C. Chest radiography, echocardiogram (ECHO), lactate, and BNP.
    D. Chest radiography, arterial line, ABG, and lactate.

3. All tests mentioned above have been ordered, and the following results are available. J.M.'s BP is 110/76 (MAP 87) mm Hg and HR is 56 beats/minute.

    - Chest radiography reveals diffuse patchy opacities; however, infiltrate cannot be ruled out; lines are all in appropriate positions.
    - Serum chemistry panel results are as follows: sodium 126 mEq/L, potassium 4.8 mEq/L, chloride 102 mEq/L, carbon dioxide 21 mEq/L, BUN 32 mg/dL, SCr 1.6 mg/dL, and glucose 134 mg/dL.
    - Results of the CBC are as follows: WBC 9.8×10^3 cells/mm^3, hemoglobin 11.1 g/dL, hematocrit 32.6%, and platelet count 173,000/mm^3.
    - Additional laboratory values include the following: troponin 0.9 ng/mL, AST 114 IU/L, ALT 102 IU/L, and BNP 1936 pg/mL.
    - Invasive hemodynamic parameters include CVP 28 mm Hg, pulmonary artery pressures 46/22 mm Hg, cardiac index 1.8 L/minute/m^2, and central venous oxygen saturation (ScvO$_2$) 53%; pulmonary artery occlusion pressure is not yet available.
    - ABG results are as follows: pH 7.36, Po$_2$ 93.7, Pco$_2$ 43.2, bicarbonate 23.9, O$_2$ saturation 89%, and lactate 6.9.
    - ECHO results are pending.

    The patient's physical examination reveals that his extremities are cold to the touch, and capillary refill is poor. The team has ordered furosemide 80 mg intravenously once and discontinued metoprolol; the team would like to initiate a vasopressor or inotrope for this patient. Which would be best to recommend at this time?

    A. Norepinephrine 0.08 mcg/kg/minute.
    B. Epinephrine 0.08 mcg/kg/minute.
    C. Milrinone 0.25 mcg/kg/minute.
    D. Dobutamine 5 mcg/kg/minute.

IV. ACUTE CORONARY SYNDROMES

A. Pathophysiology
    1. Manifestation of prolonged cessation of oxygenated blood supply to a portion of the myocardium that is most commonly caused by an acute thrombus at the site of coronary atherosclerotic stenosis leading to local or regional myocardial ischemia and necrosis
    2. Other disease states leading to an elevated myocardial oxygen demand with a concurrent inability to meet such demands may result in a scenario where "demand ischemia" is considered versus a diagnosis of ACS.

B. Presentation and Diagnosis (Circulation 2013;127:e362-425; Circulation 2014;130:e344-426) – Although other cardiac enzymes assays are available for clinical use, cardiac troponins are usually used as sensitive markers indicative of myocardial necrosis. Troponin is eliminated renally.
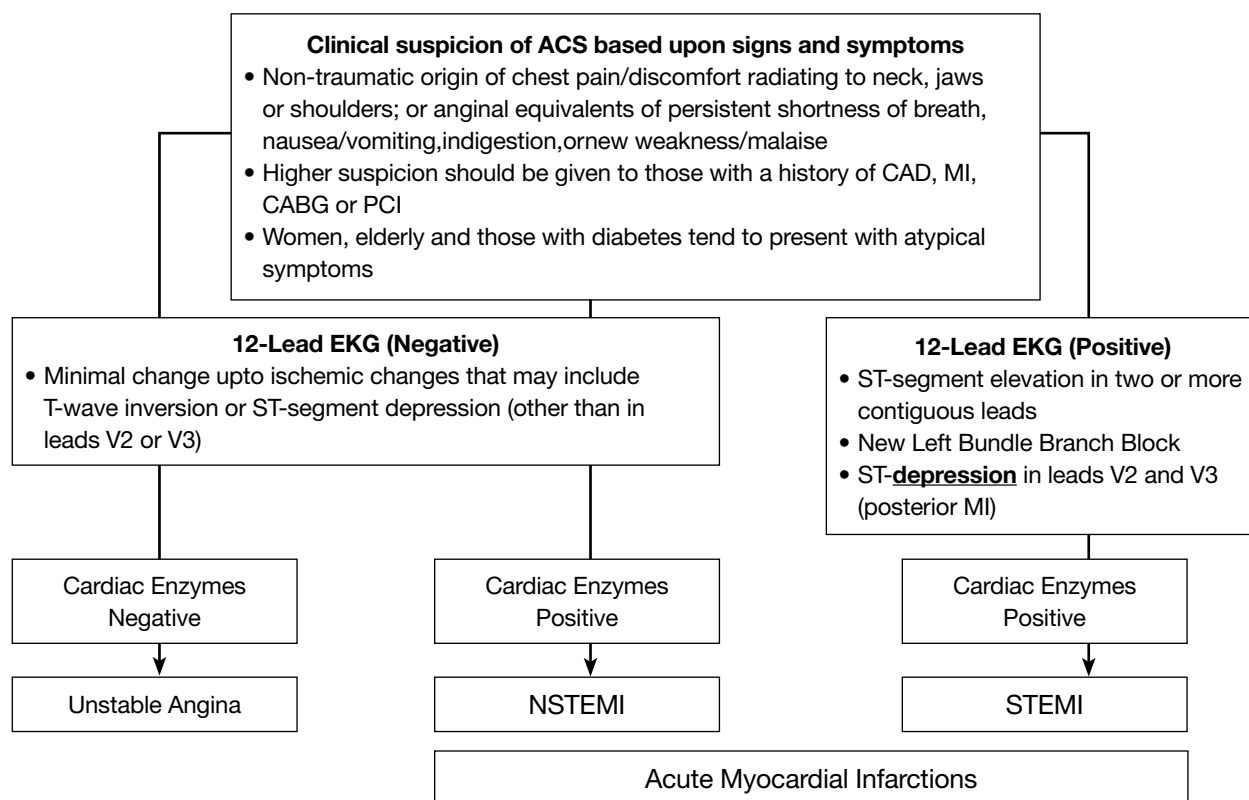
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┌─────────────────────────────────────────────────────────────────┐
│          Clinical suspicion of ACS based upon signs and symptoms  │
│  • Non-traumatic origin of chest pain/discomfort radiating to     │
│    neck, jaws or shoulders; or anginal equivalents of persistent  │
│    shortness of breath, nausea/vomiting,indigestion,ornew         │
│    weakness/malaise                                               │
│  • Higher suspicion should be given to those with a history of    │
│    CAD, MI, CABG or PCI                                           │
│  • Women, elderly and those with diabetes tend to present with    │
│    atypical symptoms                                              │
└─────────────────────────────────────────────────────────────────┘
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12-Lead EKG (Negative)
• Minimal change upto ischemic changes that may include T-wave inversion or ST-segment depression (other than in leads V2 or V3)

12-Lead EKG (Positive)
• ST-segment elevation in two or more contiguous leads
• New Left Bundle Branch Block
• ST-**depression** in leads V2 and V3 (posterior MI)

Cardiac Enzymes Negative	Cardiac Enzymes Positive	Cardiac Enzymes Positive
Unstable Angina	NSTEMI	STEMI

Acute Myocardial Infarctions

Figure 7. Presentation and diagnosis.

Box 2. Causes of Troponin Elevation (Heart 2006;92:987-93)

Acute MI	Chronic heart failure
Post-PCI	Acute decompensated heart failure
Early post-cardiac surgery	Chest wall trauma
Acute pulmonary embolism	Severe strenuous exercise
Rhabdomyolysis	Cardiotoxic chemotherapy
Tachyarrhythmia	Direct current cardioversion/defibrillation
Aortic stenosis	Cardiac amyloidosis
Pericarditis	Heart transplantation
Myocarditis	Sepsis
Type A dissection	

PCI = percutaneous coronary intervention.

C.   Acute Management of MI

Table 2. Acute Management (Circulation 2013;127:e362-425; Circulation 2014;130:e344-426)

MI Type	STEMI	NSTEMI
Goals of care	Reperfusion therapy as soon as possible • Primary PCI preferred if it can be performed within 90 min of medical contact • If primary PCI is <u>unavailable</u> within 90 min of medical contact, thrombolytics should be administered within 30 min of presentation unless contraindications exist • Surgical revascularization may be indicated, depending on severity of CAD, complexity of anatomy, or development of other complications	Prevent total occlusion of the vessel • Decision and need for revascularization (PCI or surgery) vs. medical management should be made on the basis of risk stratification, symptom resolution, and indicators of ongoing myocardial damage/ischemia

PCI = percutaneous coronary intervention.

Table 3. Predominant Interventions on Presentation/Onset for Stabilization – Any ACS (Circulation 2013;127:e362-425; Circulation 2014;130:e344-426)

Predominant interventions on presentation/onset for stabilization – Any ACS	
Oxygen	• Can help facilitate anginal pain secondary to tissue hypoxia • Supplemental oxygen considered if SaO_2 less than 90%, respiratory distress, or other high-risk features for hypoxemia
Aspirin	• Inhibit platelet activation • Four aspirin 81 mg each (324 mg total) or one 325-mg tablet (non–enteric coated) should be chewed and swallowed immediately

Nitrates	• Can facilitate coronary vasodilation and may also be helpful in scenarios of severe cardiogenic pulmonary edema caused by increased venous capacitance
	• Nitroglycerin (NTG) 0.4 mg sublingually every minute for total of THREE doses; afterward, assess need for IV NTG
	• Intravenous NTG is indicated in the first 48 hours after treatment of persistent ischemia, HF, or hypertension but should not preclude therapy such as β-blockers or ACE inhibitors when indicated
	• **Should <u>NOT</u> be administered:**
	  o If SBP < 90 mm Hg OR if SBP is ≤ 30 mm Hg below baseline
	  o If severe bradycardia (including heart block) with HR ≤ 50 beats/minute
	  o If tachycardia (HR ≥ 100 beats/minute) in the absence of symptomatic HF, or RV infarction
	  o If patient has received an oral phosphodiesterase inhibitor within the past 24–48 hours

Morphine or other narcotic analgesic	• Provides analgesia and decreases pain-induced sympathetic/adrenergic tone • Morphine commonly used because it may also induce vasodilation and mediate some degree of afterload reduction • Morphine now carries a class IIbB recommendation and may be not be favored over other narcotic analgesics, given that at least two large trials have identified an association between morphine administration and risk of death (N Engl J Med 2014;371:1016-27; Am Heart J 2005;149:1043-9)

Table 3. Predominant Interventions on Presentation/Onset for Stabilization – Any ACS *(continued)*

Predominant interventions on presentation/onset for stabilization – Any ACS		

β-Blockade	• Decreases HR and myocardial oxygen demand and increases diastolic filling time of ventricles and thereby the coronary arteries
	• **β-Blockade should be initiated within the first 24 hr of an ACS <u>unless</u>:**
	  o There are signs of HF
	  o Active evidence of other shock states
	  o If at increased risk of cardiogenic shock (SBP < 120 mm Hg), HR > 110 beats/minute or < 60 beats/minute
	• *Relative contraindications* **to β-blockade include:**
	  o PR interval greater than 0.24 s, second- or third-degree heart block, and active asthma/reactive airway disease	

Loop diuretic	• May be warranted if patient is develops severe cardiogenic pulmonary edema or other concurrent symptoms of HF with volume overload	
Helpful acronyms	MONA ± BB • Morphine • Oxygen • Nitrates (unless contraindicated) • Aspirin • β-Blocker (unless contraindicated)	LMNOP + aspirin (in reverse) • Aspirin • Positioning (resting upright + ECG) • Oxygen • Nitrates (unless contraindicated) • Morphine • Loop diuretic
Other precautions	• ACE inhibitors/ARBs should be used with caution within the first 24 hours of ACS because of the risk of hypotension and potential contribution to contrast-induced nephrotoxicity • Any NSAID other than aspirin should be avoided and/or discontinued for reasons other than GI bleeding and nephrotoxicity, which may include reinfarction, hypertension, HF exacerbation, myocardial rupture, and overall increased risk of mortality associated with their use	

GI = gastrointestinal; HF = heart failure; LMNOP = lasix-morphine-nitro-oxygen-position/positive pressure ventilation; NSAID = nonsteroidal anti-inflammatory drug.

    D. Revascularization

        1. Nonsurgical – Details of interventional cardiology procedures are too broad to be discussed in great detail in this chapter; however, following are some considerations of the intervention that may play a role in postprocedural management during a left heart catheterization and percutaneous coronary intervention (PCI):

        a. Access site

           i. Radial artery (and rarely, brachial artery) (Catheter Cardiovasc Interv 2011;78:840-6)

               (a) Easily accessible

               (b) Increased risk of vasospasm during procedure

               (c) Easily compressible vessel when hemostasis is needed postprocedure

               (d) Does not prevent patient mobility postprocedure

          ii. Femoral artery

               (a) Easily accessible

               (b) More difficult to compress vessel when hemostasis is needed postprocedure and also associated with increased bleeding complications

               (c) Limits patient mobility postprocedure for at least 12–24 hours (bleeding risk after sheath removal)

    b.   Common interventions performed:
- i.   Thrombectomy: Thrombus aspiration generally followed by placement of a stent at site of lesion
- ii.   POBA (plain old balloon angioplasty): Balloon expansion and at least temporary displacement of occlusion at site of lesion
- iii.   Stent placement
  - (a)   Important to note the number of stents placed, the types of stents, and the locations of placement
  - (b)   Bare metal stent
    - (1)   Requires aspirin for life and a P2Y12 antagonist for at least 1 month (12 months preferred) to allow adequate time for endothelialization of the stent(s)
    - (2)   Longer therapy durations may be considered, depending on the number of stents and/or location(s) of the stent(s).
    - (3)   Higher risk of in-stent stenosis over time as reendothelialization occurs
  - (c)   Drug-eluting stent
    - (1)   Requires aspirin for life and a P2Y12 antagonist for at least 12 months. Longer therapy durations may be considered, depending on the number of stents and/or location(s) of the stent(s). Ongoing investigations are evaluating the optimal duration of dual antiplatelet therapy, but many questions are currently unanswered.
    - (2)   Associated with a higher risk of stent thrombosis; the rate of endothelialization over the stent is slowed by the drug coating on the stent, thus leaving metal exposed that can potentiate thrombus formation
- iv.   Ventriculogram: Means of assessing the ejection fraction using a larger volume of intravenous contrast dye delivered directly into the ventricle to estimate the volume of blood ejected during systole

2.   Surgical revascularization – Details of coronary artery bypass grafting (CABG) procedures, including conduit type and use of cardiopulmonary bypass (or performing off-pump), are too broad to be discussed in greater detail in this chapter. According to the STS/ACC/AHA CABG guidelines, emergency CABG is recommended in patients with an acute MI in the following scenarios: (J Am Coll Cardiol 2011;58:e123-210)

    a.   Primary PCI has failed or cannot be performed

    b.   Coronary anatomy is more suitable for CABG

    c.   Persistent ischemia of a significant area of myocardium at rest and/or hemodynamic instability refractory to nonsurgical therapy is present

    d.   Requirement of surgical repair of a postinfarction mechanical complication of MI (i.e., ventricular septal rupture, mitral valve insufficiency caused by papillary muscle infarction and/or rupture, or free wall rupture)

    e.   Patients with cardiogenic shock who are suitable for CABG, irrespective of the time interval from MI to onset of shock and time from MI to CABG

    f.   Patients with life-threatening ischemic ventricular arrhythmias in the presence of a left main stenosis of 50% or more and/or three-vessel CAD

    g.   CABG use is reasonable as a revascularization strategy in patients with multivessel CAD with recurrent angina or MI within the first 48 hours of STEMI presentation as an alternative to a more delayed strategy

    h.   Early revascularization with PCI or CABG is reasonable for select patients older than 75 years with ST-segment elevation or left bundle branch block who are suitable for revascularization irrespective of the time interval from MI to onset of shock

3. Medical management – No revascularization:
   a. Less invasive strategies may be opted for rather than revascularization in some patients. Considerations reinforce a patient-centered approach driven by evidence of ongoing/recurrent ischemia and feasibility of revascularization, including myocardial viability, patient frailty, and comorbid disease states.
   b. Ongoing care outlined in section E remains the focus of optimizing aggressive medical management.

E. Antithrombotics in MI
   1. The roles and combinations of antithrombotics continue to be refined in select populations (those with NSTEMI/ACS, STEMI, and PCI). For the most current guidelines and landmark trials, please see www.acc.org/guidelines.
   2. Oral antiplatelet therapy
      a. Platelets can be activated by several different mechanisms, only some of which can be inhibited by medications.
      b. In the critically ill, our ability is currently limited to assess and interpret the adequacy of antiplatelet therapies. Clinical evidence with platelet function testing has not been well-studied with durable clinical endpoints such as cardiac events and/or mortality.
      c. Common clinical obstacles in the critically ill are without evidence-based solutions at this time; these include variability in drug response that could be owing to absorption and metabolism variability in patients with hepatic insufficiency. Furthermore, therapeutic alternatives are limited and without evidence when enteral administration is not an option.

Table 4. Oral Antiplatelet Therapy[a] (Circulation 2013;127:e362-425; Circulation 2014;130:e344-426; J Am Coll Cardiol 2011;58:e123-210; J Am Coll Cardiol 2011;58:e44-122; Br J Clin Pharmacol 2011;72:647-5)

Medication	Aspirin	Clopidogrel	Prasugrel	Ticagrelor
Role/mechanism of inhibition	Inhibits thromboxane A_2–mediated platelet activation and aggregation	Inhibits ADP-mediated platelet aggregation ($P2Y_{12}$ receptor) to prevent conformational change of GPIIb/IIIa receptor	Inhibits ADP-mediated platelet aggregation ($P2Y_{12}$ receptor) to prevent conformational change of GPIIb/IIIa receptor	Inhibits ADP-mediated platelet aggregation ($P2Y_{12}$ receptor) to prevent conformational change of GPIIb/IIIa receptor
Loading dose	324–325 mg	600 mg	60 mg	180 mg
Maintenance dose	81 mg	75 mg QD	10 mg QD	90 mg BID
Route	Oral	Oral	Oral	Oral
Prodrug	No	Yes	Yes	No
Reversible platelet binding	No	No	No	Yes
Onset	30 min	2 hours	30–60 min	30–60 min
% Platelet inhibition	~20	40	70	95
Recommended holding duration before CABG[b]	Do not hold	5 days	7 days	7 days
Other notable adverse effect(s) or clinical pearls		• Pharmacogenomic variance has been noted and may contribute to drug response	• Black box warning against use in patients with a history of stroke or TIA, and warning of use in patients > 75 years or weight < 60 kg	• Adenosine-induced bradycardia and dyspnea • Elderly patients and patients with moderate or severe hepatic impairment may be at increased risk of bleeding • Concomitant doses of ASA > 100 mg should be avoided

[a]Note: Ticlopidine is not widely used in therapy anymore or discussed in the most current ACS guidelines.

[b]Decisions to hold these agents before other invasive procedures must consider indications for use, risk of thrombosis (i.e., stent type, locations, and number), and risk of bleeding associated with intended procedure/surgery. (J Am Coll Cardiol 2011;58:e44-122; JAMA 2013;310:1451-2; Catheter Cardiovasc Interv 2013;82:1113-4; JAMA 2013;310:189-98; J Am Coll Cardiol 2007;49:734-9; N Engl J Med 2013;368:2113-24; Reg Anesth Pain Med 2010;35:64-101).

ADP = adenosine diphosphate; ASA = acetylsalicylic acid; BID = twice daily; GP = glycoprotein; QD = once daily; TIA = transient ischemic attack.

    3. Parenteral antithrombotics
        a. Use of these agents is most intensive in the procedural setting, although may continue for a finite period postprocedurally
        b. The selection and use among the agents in Table 5 may depend on presentation, timing/dose of preprocedural antiplatelet medication administration, clot burden during procedure, and estimated bleeding risk of the procedure.

Table 5. Parenteral Antithrombotics (Circulation 2013;127:e362-425; Circulation 2014;130:e344-426; J Am Coll Cardiol 2011;58:e123-210; J Am Coll Cardiol 2011;58:e44-122; Br J Clin Pharmacol 2011;72:647-57)

Medication	Heparin (UFH)[a]	Bivalirudin	Abciximab	Eptifibatide	Tirofiban
Role in therapy	Indirect thrombin inhibition mediates decreased propagation of clot	Direct thrombin inhibitor – mediates decreased propagation of clot	Binds to GPIIb/IIIa platelet receptor, preventing platelet binding to fibrinogen	Binds to GPIIb/IIIa platelet receptor, preventing platelet binding to fibrinogen	Binds to GPIIb/IIIa platelet receptor, preventing platelet binding to fibrinogen
Loading dose	50–100 units/kg bolus	0.75 mg/kg	0.25 mcg/kg	180 mg/kg	25 mcg/kg
Continuous infusion	Variable (if used)	1.75 mg/kg/hr	0.125 mcg/kg/min (max 10 mcg/min)	2 mcg/kg/min	0.15 mcg/kg/min
Platelet inhibition	N/A	N/A	Irreversibly inhibits for the life of the platelet (7–10 days)	Restoration of platelet function within 6–8 hours of discontinuation	Restoration of platelet function within 6–8 hours of discontinuation
Elimination	• Hepatic and reticulo-endothelial system	• 80% plasma proteolysis • 20% renal	• Plasma elimination	• 50%–71.4% renal	• Renal
Removed by dialysis	No	Yes	No	Yes	Yes
Other notable adverse effect(s) or clinical pearls	• Cannot be used in patients with a history/suspicion of heparin – induced thrombocytopenia (HIT) • Target activated clotting time (ACT) or 200–250 s during procedure	• Requires renal dose adjustment • Can be used in patients with or without a history or suggestion of HIT • May be preferred in patients with higher bleeding risk • Target ACT or 200–250 s during procedure	• Murine monoclonal antibody – may produce antigenicity	• Requires renal dose adjustment	• Requires renal dose adjustment

[a]Enoxaparin may be used rather than UFH.

HIT = heparin-induced thrombocytopenia; UFH = unfractionated heparin.
  o If age younger than 75 years: 30 mg intravenous push within 15 minutes, followed by 1 mg/kg subcutaneously, followed by every 12 hours (max 100 mg for the first two doses)
  o If 75 years or older: 0.75 mg/kg subcutaneously every 12 hours (max 75 mg for the first two doses)

F. Postintervention Complications
   1. Bleeding (particularly retroperitoneal bleeding)
      a. Several antithrombotic agents are used during PCI to inhibit both the platelets and the clotting cascade, causing potential coagulopathies.
      b. In addition to antithrombotic use, the catheterization access site (radial vs. femoral) has been identified as a major contributor to post-PCI bleeding complications.
   2. Dissection/rupture of free wall, coronary artery, or aorta: Although this may be spontaneous, it may also be caused by vessel trauma from the catheter itself.
   3. Stent thrombosis
      a. When antiplatelet therapy is discontinued early (aspirin, P2Y12, or both), stent thrombosis may occur in up to 25% of coronary artery stents, irrespective of type of stent (drug-eluting stent or bare metal stent).
      b. Almost 1 in 7 patients may discontinue $P2Y_{12}$ inhibitors within 30 days post-PCI, thus increasing mortality risk (adjusted hazard ratio 9.0; 95% CI, 1.3–60.6). (JAMA 2013;310:189-98)
      c. Mortality rates associated with stent thrombosis can be as high as 45%.
      d. Despite bleeding risks in critically ill patients, careful consideration should be given to correlating these risks with the risk of stent thrombosis.
   4. Papillary muscle rupture and mitral regurgitation
   5. Arrhythmias (particularly after reperfusion)
   6. Contrast-induced nephropathy

G. Ongoing Care – Quality measures for NSTEMI or STEMI independent of revascularization or medical management
   1. Medications that should be initiated before discharge or contraindications should be documented in the medical record.
      a. Aspirin
      b. Statin
      c. $P2Y_{12}$ inhibitor
      d. β-Blocker
      e. If LVEF is less than 40%, ACE inhibitor or ARB and spironolactone
   2. Interventions and/or referrals
      a. LV function assessment (by imaging or during catheterization)
      b. Cardiac rehabilitation
      c. Smoking cessation counseling
      d. Measurement of a lipid profile, including the LDL (low-density lipoprotein) cholesterol, should preferably be obtained within 24 hours of admission. Any lipid profile measured between 6 months before first medical contact and hospital discharge qualifies for this quality measure.
   3. For more information on cardiology-related quality measures and registries, see https://www.ncdr.com/.

Patient Case *(see p. 1-190 for case information)*

4. J.M.'s ECG results reveal no notable evidence of ST-segment changes. The resident is still considering a diagnosis of an ACS, given the patient's shortness of breath and troponin elevation. Which would be most accurate regarding whether any other potential explanations exist for these diagnostic criteria?

    A. No, this is most likely an NSTEMI.
    B. Yes, it is likely undiagnosed chronic obstructive pulmonary disease.
    C. Yes, it is likely early sepsis.
    D. Yes, it is likely decompensated heart failure.

5. J.M. has been experiencing intermittent HR pauses on telemetry. The team has consulted the cardiac electrophysiology team. In the meantime, which statement most accurately reflects whether any other underlying correctable/contributing causes can be addressed?

    A. Ticagrelor should be discontinued, and J.M. should be switched to clopidogrel.
    B. Ticagrelor should be discontinued; only aspirin is needed for J.M.'s CAD at this time.
    C. There are no other identifiable causes, and this is likely a reflection of J.M.'s heart failure disease progression.
    D. J.M.'s hyperkalemia should be treated.
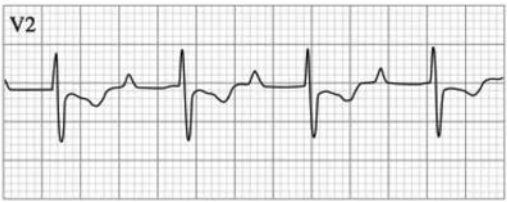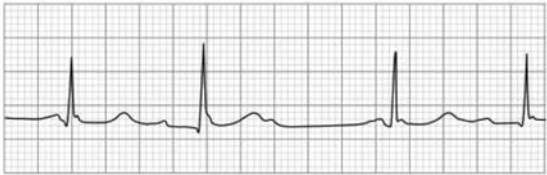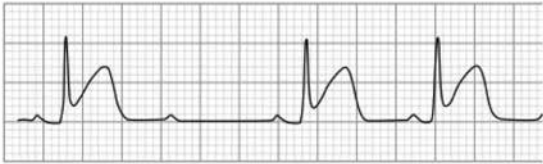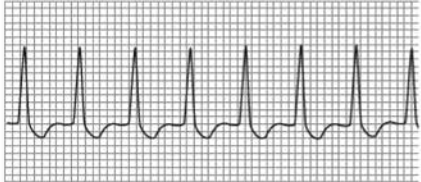
V. ARRHYTHMIAS AND ANTIARRHYTHMICS

A. Pathophysiology: Arrhythmias are generally caused by impulse formation and/or conduction abnormalities.

B. Bradyarrhythmias and Types of Heart Block (beyond sinus) (2011;xiv, 461 p.; 2014;xix, 1490 p.; BMJ 2002;324:662-5; BMJ 2002;324:415-8)
   1. Etiologies of heart block

Box 3. Causes of Bradycardias

- Drug toxicity
- CAD
- Degenerative conduction disease
- Surgery (particularly cardiac surgery)
- Endocarditis
- Electrolyte disturbances (particularly hyperkalemia)
- Vagal nerve mediated heart block
- Tumors
- Myocarditis

   2. When evaluating ECGs in the presence of heart block, QRS complex evaluation can guide some differential diagnoses to the source of conduction problems (see Table 6).
       a. Narrow QRS complexes commonly indicate AV nodal dysfunction.
       b. Wide QRS complexes may indicate dysfunction in either the AV node or the His-Purkinje system.

Table 6. Bradyarrhythmias and Types of Heart Block (2011;xiv, 461 p.; 2014;xix, 1490 p.; BMJ 2002;324:662-5; BMJ 2002;324:415-8)

Type	ECG Example	Description
First degree	V2	• Delayed conduction from the sinoatrial (SA) node to the atrioventricular (AV) node characterized by a P-R interval > 0.2 s • Relatively benign, however underlying contributors should be evaluated and minimized (i.e., β-blockers and other agents)
Second-degree Mobitz type 1 (Wenckebach)		• Consistent P-P interval with progressive prolongation of the P-R (indicating impaired SA to AV node conduction) eventually resulting in absence of a QRS complex because of the lack of AV node conduction of atrial impulse • Of most concern in elderly patients where this may be indicative of progressive conduction disease; may be more benign in younger patients • "Longer, longer, longer, drop....must be Wenckebach"
Second-degree Mobitz type 2	(in a post-ACS setting)	• Consistent P-P interval and consistent P-R interval duration with spontaneous absence of a QRS complex because of the lack of AV node conduction of atrial impulse • Usually indicative of more significant conduction disease and be associated with syncope, heart failure, and increased mortality rates
Third degree		• Characterized by consistent P-P intervals, R-R intervals, and variable/random P-R interval representing independent, uncoordinated atrial and ventricular conduction
Junctional rhythm		• Manifested when sinus node dysfunction allows the AV node to take over as the active cardiac pacemaker resulting in retrograde conduction through the atria

3. Management of bradyarrhythmias includes three principal strategies (see also Figure 5). Stabilize the patient, if symptomatic.
   a. Consider atropine for temporary correction to decrease vagal tone.
   b. Consider pacing strategies (temporary transvenous pacer, transcutaneous pacer, pacing pulmonary artery catheter). Interrogate permanent pacemaker for malfunction/optimization.
   c. Consider chronotropic β-agonist infusion.
      i. Isoproterenol
      ii. Dobutamine
      iii. Epinephrine
      iv. Dopamine
   d. Identify and treat underlying causes/toxidromes.

Adult Bradycardia
(With Pulse)

1. Assess appropriateness for clinical condition. Heart rate typically <50/min if bradyarrhythmia.

2. **Identify and treat underlying cause**
   - Maintain patent airway; assist breathing as necessary
   - Oxygen (if hypoxemic)
   - Cardiac monitor to identify rhythm; monitor blood pressure and oximetry
   - IV access
   - 12-Lead ECG if available; don't delay therapy

3. **Persistent bradyarrhythmia causing:**
   - Hypotension?
   - Acutely altered mental status?
   - Signs of shock?
   - Ischemic chest discomfort?
   - Acute heart failure?

4. No → **Monitor and observe**

5. Yes → **Atropine**
   If atropine ineffective:
   - Transcutaneous pacing
     OR
   - **Dopamine** infusion
     OR
   - **Epinephrine** infusion

6. **Consider:**
   - Expert consultation
   - Transvenous pacing

Doses/Details

Atropine IV Dose:
First dose: 0.5 mg bolus
Repeat every 3-5 minutes
Maximum: 3 mg

- Search for and treat possible contributing factors:
  – Hypovolemia   – Toxins
  – Hypoxia   – Tamponade, cardiac
  – Hydrogen ion (acidosis) – Tension pneumothorax
  – Hypo-/hyperkalemia – Thrombosis (coronary or pulmonary)
  – Hypoglycemia   – Trauma (hypovolemia, increased ICP)
  – Hypothermia

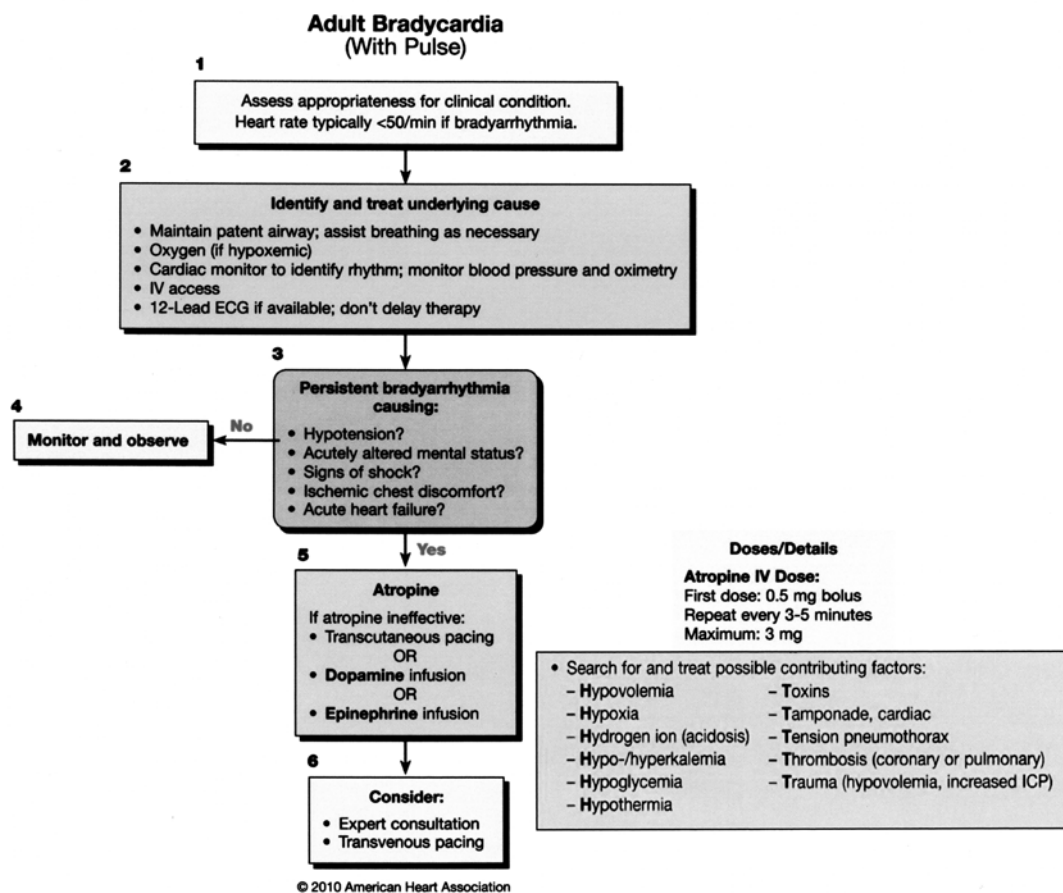© 2010 American Heart Association

Figure 8. Advanced cardiac life support bradycardia algorithm. (Circulation 2010;122:S729-6)

C. Tachyarrhythmias (beyond sinus) – Etiologies and hemodynamic consequences
   1. Etiologies of tachyarrhythmias
      a. Usually related to enhanced automaticity, reentry, or triggered activity
      b. A history that includes ischemic heart disease or congestive cardiac failure is 90% predictive of VT.
   2. In evaluating ECGs for tachyarrhythmias, some fundamental considerations include:
      a. Evaluate for the presence of P waves.
      b. Evaluate the width of the QRS complex.

Table 7. Tachyarrhythmias (beyond sinus)[a] (Circulation 2014;130:2071-104; BMJ 2002;324:594-7; BMJ 2002;324:776-9; BMJ 2002;324:1264-7; BMJ 2002;324:1201-4; Circulation 2012;125:381-9; Heart Fail Rev 2014;19:285-93)

Supraventricular Tachyarrhythmias				
Type	Rhythm	P-wave Attributes	Atrial Rate (bpm)	Description
Premature atrial contractions (PACs)	Irregular	N/A	N/A	• Generally benign but may be more evident with increased sympathetic tone, stress, and pericarditis or with sympathomimetic use • In some cases, can lead to an AV block or initiate an reentrant SVT or AF

Supraventricular tachycardia (SVT)	Regular	Hidden or can be retrograde	140–250	• Usually sudden onset/offset with narrow QRS complexes
				• Often caused by reentry within the atrium or AV node, or by means of an accessory conduction pathway
				• Can be subcategorized as:
				  o AV nodal reentrant tachycardia (AVNRT)
				  o AV reentrant tachycardia (AVRT)
				  o Sinus node reentry tachycardia

Atrial flutter (AFl)	Regular	Saw-tooth appearance	180–350	• Generally conducts through the ventricles in a 2:1 fashion, resulting in ventricular rates of 100–150 beats/min • In some scenarios, slowing the atrial rate may increase the number of conducted beats leading to rapid ventricular rates and potential hemodynamic compromise • Associated with increased risk of stroke
Atrial fibrillation (AF)	Irregular	No distinct P wave visible	Unable to determine	• Most common arrhythmia, characterized by irregular ECG appearance because of multiple reentry circuits and ectopic foci • Often associated with structural heart disease and potentiated by increase left atrial pressures among other influencing contributors such as age, inflammation, and sympathetic tone • Associated with increased risk of stroke
Multifocal atrial tachycardias (MATs)	Irregular	> 3 different types of distinct P waves	100–130	• Can be misdiagnosed as AF • Commonly associated with respiratory disease, heart failure, critical illness • May be exacerbated by electrolyte abnormalities or toxicity with digoxin or theophylline

Table 7. Tachyarrhythmias (beyond sinus)[a] *(continued)*

Ventricular Arrhythmias	
Type	**Description**
Premature ventricular contractions (PVCs)	• Results from an ectopic ventricular focus conduction that can be identified by the lack of a preceding P wave. Commonly benign or asymptomatic, but may be of concern if present in patterns or in patients with advanced heart disease 　o Bigeminy: Every other beat is a PVC 　o Trigeminy: Every third beat is a PVC 　o Couplets: Patterns of two consecutive PVCs 　o Triplets: Patterns of two consecutive PVCs
Ventricular tachycardia (VT)	• Potentially lethal wide QRS complex tachycardia characterized according to morphology and duration. Can degenerate into VF or asystole 　o *Monomorphic VT:* When every QRS complex appears the same and the rate is regular (100–200 beats/min). Commonly caused by reentry circuit related to myocardial scar or fibrosis 　o Polymorphic: When the QRS complexes continually vary in shape and rate. May be related to multiple ectopic foci, myocardial ischemia, or torsades de pointes 　o *Non-sustained VT:* Self-terminating episodes lasting for < 30 s 　o *Sustained VT:* If VT persists for more than 30 s, produces severe symptoms, including syncope, or requires termination by administration of an antiarrhythmic drug or direct cardioversion/defibrillation
Ventricular fibrillation (VF)	• Life-threatening arrhythmia with a chaotic ECG with no discernible QRS, representing rapid disorganized conduction with no resultant coordinated ventricular contractions

[a]Other arrhythmias beyond the scope of this review include sick sinus syndrome (tachy-brady syndrome) and Wolfe-Parkinson-White.

   3. Management of tachyarrhythmias with a pulse includes the following strategies:
      a. Stabilization of patient: See Figure 6 and Cardiovascular Emergencies chapter.
      b. Long-term control strategies
         i. Atrial tachyarrhythmias
            (a) HR control typically with class II agents, class IV agents, and/or digoxin (see Table 8)
            (b) Heart rhythm control
               (1) Catheter-based ablation
               (2) Surgical ablation
               (3) Antiarrhythmic therapy typically with class IC or class III agents (see Table 8)
         ii. Ventricular tachyarrhythmias
            (a) Catheter ablation
            (b) Antiarrhythmic therapy
            (c) Evaluation for implantable cardioverter-defibrillator.
      c. Overall considerations for antiarrhythmics (see Table 8) (Circulation 2014;130:2071-104; BMJ 2002;324:594-7; BMJ 2002;324:776-9; BMJ 2002;324:1264-7; BMJ 2002;324:1201-4; Circulation 2012;125:381-9; Heart Fail Rev 2014;19:285-93)
         i. Abrupt discontinuation of chronic antiarrhythmics (i.e., chronic medication before ICU admission) should be done with caution and awareness of antiarrhythmic indication as well as risks-benefits of continuation/cessation.

    ii. Appropriate monitoring and potential adjustment may be warranted with many of these agents in the critically ill patient.

        (a) QT/QTc prolongation increases the risk of torsades de pointes. This risk can be influenced not only by the absolute duration of the QT/QTC, but also by the rate at which the QT/QTc is changed (i.e., faster change may also increase risk).

        (b) The class III antiarrhythmics sotalol and dofetilide can be used for both atrial and ventricular tachyarrhythmias and, because of some notable characteristics, should be watched closely when used in the critically ill.

           (1) Both are renally eliminated.

           (2) Both have notable interactions with several other medications in addition to their effect on the QT/QTc interval.

           (3) ECG monitoring should be performed for safety and tolerability 2–3 hours after the first five doses when initiating, reinitiating, or introducing another interacting or QT-prolonging agent.

           (4) Electrolyte abnormalities may place a patient at increased risk of torsades de pointes (particularly magnesium and potassium).
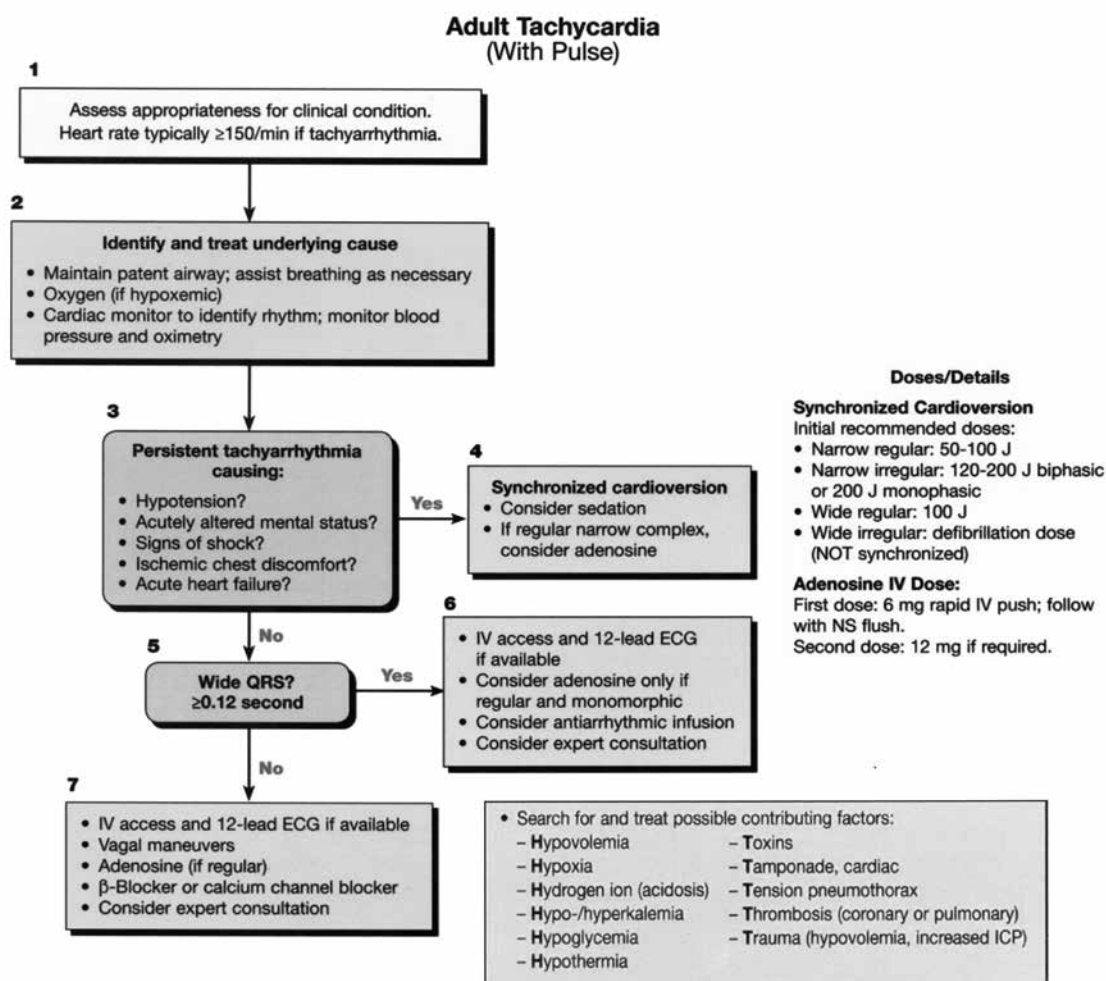

Figure 9. Advanced cardiac life support tachycardia algorithm (Circulation 2010;122:S729-67).

iii. Common agents in the ICU
   (a) β-Blockade
      (1) May be of limited use in patients receiving vasopressors, but can be used for both atrial and ventricular tachyarrhythmias
      (2) Esmolol has the shortest half-life (cleared by plasma esterases), and administration rates commonly coincide with high volumes of fluid.
      (3) Agents with combined α_1-antagonism and non-selective β-antagonism will have greater effects on BP compared with their β_1-specific antagonist counterparts.
         • β_1-specific antagonist examples:
            ○ Esmolol (intravenous), metoprolol tartrate (oral/intravenous)
         • Combined α1- and non-selective β-antagonist examples:
            ○ Carvedilol (oral) – 1α:10β receptor activity
            ○ Labetalol (intravenous) – 1α:7β receptor activity
            ○ Labetalol (oral) – 1α:3β receptor activity
   (b) Diltiazem
      (1) May be of limited use in patients on vasopressors, but can be used for both atrial and ventricular tachyarrhythmias
   (c) Non-dihydropyridine calcium channel blockers are not recommended in patients with heart failure with reduced ejection fraction (HF*r*EF) (systolic heart failure) (class III C). (J Am Coll Cardiol 2013;62:e147-239)
   (d) Amiodarone
      (1) Widely versatile and commonly used for both atrial and ventricular tachyarrhythmias
      (2) Affects all phases of the action potential (Na, Ca, K channel and provides some α- and β-antagonism)
      (3) Severe hypotension can occur because of the solvent polysorbate 80 (Tween 80) used in some formulations. This transient hypotension in patients with a pulse can be associated with rapid infusions, particularly of undiluted drugs, and is best avoided by dilution and slower administration. However, in pulseless patients, rapid administration of undiluted amiodarone is commonly indicated.
      (4) Among common agents used in the ICU, amiodarone has one of the largest volumes of distribution (about 60 L/kg) and prolonged half-lives (50–55 days).
      (5) In adults, common total intravenous or oral loading doses over several days are about 8–10 g before switching to a maintenance dose.
            ○ 7.2–12 g = (1.5–2.5 mg/L) × (60 L/kg) × (80 kg)
      (6) Extensive metabolism by CYP3A4 and CYP2C8 and enzyme inhibitor of CYP3A4, CYP1A2, CYP2C9, and CYP2D6, resulting in several drug-drug interactions
      (7) Therapeutic drug monitoring by levels of amiodarone or its metabolite, *N*-desethylamiodarone, is rarely warranted unless trying to confirm suspected toxicity
      (8) If patients are to be continued on amiodarone for a prolonged duration, thyroid and liver function tests, pulmonary function tests, chest radiographs, and ophthalmic examinations should be evaluated periodically. (Heart Rhythm 2007;4:1250-9)
   (e) Lidocaine
      (1) Indicated only for ventricular tachyarrhythmias and is particularly useful if the tachyarrhythmia is caused by active ischemic myocardial tissue
      (2) Efficacy and toxicity are both concentration-dependent.

(3) Metabolism is largely dependent on hepatic blood flow; the primary metabolites are monoethylglycinexylidide (MEGX) and glycine xylidide (GX) and are mediated by CYP1A2. Both lidocaine and MEGX contribute to therapeutic effect and toxicity, whereas GX has predominantly toxic adverse effects. Lidocaine's metabolites are eliminated renally.

(4) Concentration-dependent protein binding includes about 25% bound to albumin and about 50% bound to α_1-acid glycoprotein (AAG).

(5) As AAG increases and decreases as an acute-phase reactant within the first 12–72 after certain stresses (i.e., acute MI, heart failure exacerbation, trauma), an unsuspected variation can occur in free lidocaine levels. Because of the toxicity profile and concentration-dependent efficacy, routine levels should be monitored in most patients if lidocaine is to be continued beyond 24 hours (particularly in patients with heart failure, liver disease, and renal dysfunction).

Box 4. Lidocaine Levels and Toxicity Symptoms

Total Serum Concentration	Toxicity
< 1.5–5 mg/L	Typical therapeutic goal level with idiosyncratic reactions
> 5–8 mg/L	Increasing risk of light-headedness, confusion, dizziness, tinnitus, twitching, tremor, blurred or double vision, hypotension, and bradycardia
> 8 mg/L	High risk of seizures, respiratory depression, hypotension, bradycardia, AV nodal blockade, decreased cardiac output

(f) Digoxin

(1) Commonly, a last-line rate control therapy for patients whose rhythm control strategies have failed and who cannot tolerate, or have contraindications to, β-blockers and/or calcium channel blockers. Some interest has also been revived in its use for heart failure to avoid hospitalization.

(2) Use for AF should be done with caution. Two recently published retrospective trials have shown considerable evidence for increased hospitalization rates and risk of death.
- 71% increased risk of death (hazard ratio 1.71; 95% CI, 1.52–1.93) and 63% increased risk of hospitalization (hazard ratio 1.63, 95% CI, 1.56–1.71) (Circ Arrhythm Electrophysiol 2015;8:49-58)
- Digoxin-treated patients had higher mortality rates (95 vs. 67 per 1000 person-years; p<0.001), and use was independently associated with mortality, despite multivariate adjustment (hazard ratio 1.26; 95% CI, 1.23–1.29, p<0.001). (J Am Coll Cardiol 2014;64:660-8)
- Eliminated renally; thus, may pose risks of digoxin toxicity in patients with acute or chronic renal failure

(3) Although the volume of distribution is relatively large (7–10 L/kg in healthy adults), only a small percentage of total body stores are present in the serum.

(4) Digoxin has a smaller volume of distribution in patients with renal failure (around 4.5 L/kg); thus, loading doses are commonly lower in these patients.

(5) Digoxin efficacy and toxicity do not correlate well with drug levels.
- Common therapeutic targets for HR control are 0.8–1.5 ng/mL, although many clinical laboratories report therapeutic levels within a 0.5–2.0 ng/mL.
- Toxicity, which can present at any serum level, should be evaluated according to clinical manifestations, including mental status changes, visual disturbances, nausea, vomiting, ventricular arrhythmias, bradycardia, and hyperkalemia.
- Efficacy is largely based on clinical control of the HR; steady-state levels (more than 5–7 days after initiation) are typically used only to validate that levels are not supratherapeutic.

4. Anticoagulation for AF or atrial flutter
   a. According to the 2014 AHA/ACC/HRS AF guidelines, all patients with atrial flutter or paroxysmal, persistent, or permanent AF should be evaluated for anticoagulation needs, preferably using the CHA_2DS_2-VASc score to approximate stroke risk (Circulation 2014;130:2071-104).
      i. Patients with a $CHADS_2$ score (congestive heart failure, hypertension, age older than 75, diabetes, and prior stroke or transient ischemic attack) and a CHA_2DS_2-VASc score of 2 or greater should be evaluated for anticoagulation.
      ii. It is reasonable to omit anticoagulation in patients with a $CHADS_2$ and CHA_2DS_2-VASc score of zero.
      iii. For patients with AF and a mechanical prosthetic heart valve or valves, bridging with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) should be performed in the context of bleeding versus stroke risk. Warfarin anticoagulation and international normalized ratio (INR) goals should be consistent with the type and location of the prosthetic valve.
      iv. Although the $CHADS_2$ and CHA_2DS_2-VASc scores are commonly used to estimate annual stroke risk, these scoring systems were not founded in the context of critically ill patients.

Box 5. $CHADS_2$ and CHA_2DS_2-VASc Stroke Risk Scores in AF (Circulation 2014;130:2071-104)

Risk Assessment	Score	Total Patient Score	Adjusted Annual Stoke Rate
$CHADS_2$		0	1.9%
• Heart failure	1	1	2.8%
• Hypertension	1	2	4.0%
• Age ≥ 75	1	3	5.9%
• Diabetes	1	4	8.5%
• Stroke, TIA, thromboembolism	2	5	12.5%
		6	18.2%
CHA_2DS_2-VASc		0	0%
• Congestive heart failure	1	1	1.3%
• Hypertension	1	2	2.2%
• Age ≥ 75	2	3	3.2%
• Diabetes	1	4	4.0%
• Stroke, TIA, thromboembolism	2	5	6.7%
• Vascular disease	1	6	9.8%
• 65–74 years	1	7	9.6%
• Sex category (female)	1	8	6.7%
		9	15.2%

TIA = transient ischemic attack.

b. Anticoagulation decisions should balance the risk of stroke versus the risks of bleeding in the context of duration of bridging and/or lack of anticoagulation. Two scoring systems for bleeding risk systems have been described to help assess bleeding risk in anticoagulation decisions for patients with AF on **warfarin** anticoagulation. Not unlike stroke risk scoring systems, these scoring systems were not founded in the context of critically ill patients.

Box 6. HASBLED or HEMOR$_2$RHAGES Bleeding Risk Scores in AF

Risk Factor Assessment	Score	Total Patient Score	Bleeds/100 Patient-Years of Warfarin
HASBLED			
• Hypertension	1	0	1.13
• Abnormal renal or liver function (1 point each)	1 or 2	1	1.02
• Stroke	1	2	1.88
• Bleeding	1	3	3.74
• Labile INRs	1	4	8.70
• Elderly (> 65 years)	1	5	12.5
• Drugs or alcohol (1 point each)	1 or 2	6	0
		Any score	1.56
HEMOR$_2$RHAGES			
• Hepatic or renal disease	1	0	1.9
• Ethanol abuse	1	1	2.5
• Malignancy	1	2	5.3
• Older age	1	3	8.4
• Reduced platelet count or function	1	4	10.4
• Rebleeding risk	2	≥ 5	12.3
• Hypertension (uncontrolled)	1	Any score	4.9
• Anemia	1		
• Genetic factors	1		
• Excessive fall risk	1		
• Stroke	1		

c. In the critically ill, parenteral anticoagulation with UFH or LMWH may be more favorable if the benefit of anticoagulation exceeds the risk of bleeding. UFH infusions would be favored over LMWH in renal failure (creatinine clearance [CrCl] less than 30 mL/minute).

d. For anticoagulation of most critically ill patients, oral anticoagulation may be less favorable or even detrimental compared with parenteral anticoagulation.

   i. Elimination of apixaban, dabigatran, and rivaroxaban is significantly affected in renal compromise, and these agents currently lack data for safety in patients with a CrCl less than 30 mL/minute at any dose. These agents interact and are currently irreversible in a controlled, expeditious fashion if the patient needs an invasive procedure or develops an acute bleed.

   ii. Warfarin presents potential difficulty because of its influence on malnutrition, drug interactions, and unpredictable dose response in the critically ill. Complications with this agent are more predictably managed compared with those with other oral anticoagulants if a patient needs an invasive procedure or develops an acute bleed, but warfarin use is still not without risk.

e. For patients with AF/flutter for 48 hours or more (or if undetermined) without therapeutic anticoagulation, absence of thrombus on the left side of the heart should be confirmed by transesophageal ECHO before pharmacologic or direct current cardioversion.

f. If AF/flutter for more than 48 hours or an unknown duration that requires direct current or pharmacologic cardioversion for hemodynamic instability, anticoagulation should be initiated as soon as possible and continued for at least 4 weeks after cardioversion unless contraindicated

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Patient Cases

Question 6 pertains to the case on 1-190.
The appropriate intervention has been made from question 5, and the patient has not required any pacing device intervention. For the next 48 hours, J.M. continues on inotrope therapy and is being diuresed (he has been 1250 and 900 mL negative, respectively, over these two days). The transthoracic ECHO results have revealed that J.M.'s ejection fraction is 15–20%, with a dilated, hypokinetic LV; severe mitral regurgitation; and dilated atria. No evidence of intracardiac thrombus is seen, but cannot be ruled out.

6. J.M. has had increasing premature atrial contractions on telemetry, and his HR has consistently been between 83 and 96 beats/minute; he is currently taking dobutamine at 5 mcg/kg/minute and a furosemide infusion at 10 mg/hour. The team is notified that J.M. has gone into AF with rapid ventricular response and an HR of 132 beats/minute (he has been in AF for about 30 minutes). His BP is now 83/52 mm Hg. Which treatment plan would be most favorable for this patient?
    A. Synchronized cardioversion.
    B. Metoprolol 5 mg intravenous push.
    C. Adenosine 6 mg rapid intravenous push through the most proximal port on the central venous catheter.
    D. Amiodarone 150 mg intravenous push, followed by a continuous infusion at 1 mg/minute.

7. M.B., a 76-year-old woman, is now in sinus rhythm with an HR of 98 beats/minute after being cardioverted this morning by direct current cardioversion for AF with rapid ventricular response and hemodynamic instability. Her medical history includes an unspecified arrhythmia, hypertension, frequent epistaxis, and diabetes. Her calculated CHA_2DS_2-VASc score is 5, and her HASBLED score is 4. The physician is considering anticoagulation with a heparin infusion while the patient is in the ICU and asks for a recommendation. Which is the most appropriate response?
    A. According to these scores, the patient's risk of bleeding exceeds her risk of stroke; thus, it would be reasonable to withhold anticoagulation.
    B. According to these scores, the patient's risk of stroke exceeds her risk of bleeding; therefore, it would be reasonable to initiate heparin anticoagulation.
    C. The HASBLED score is less relevant because it is derived from warfarin anticoagulation; however, anticoagulation is likely warranted, given the patient's CHA_2DS_2-VASc score and cardioversion this morning.
    D. The HASBLED score, CHA_2DS_2-VASc score, and cardioversion are irrelevant to this patient's current care, and because she remains in sinus rhythm, anticoagulation is not warranted.

VI. HEART FAILURE

A. Clinical Syndrome – Manifested because of congenital or acquired structural or functional myocardial dysfunction that impairs filling and/or emptying of the heart
   1. Mortality rate of 50% with 5 years of diagnosis
   2. Predominantly descriptive of LV and its pump performance and the ejection fraction
   3. Prognosis and treatment of heart failure are largely dependent on the etiology and symptomology.

Table 8. Diastolic Dysfunction vs. Systolic Dysfunction in Heart Failure

Type	Heart Failure with _preserved_ EF (HF*p*EF)	Heart Failure with _reduced_ EF (HF*r*EF)
Dysfunction	• Diastolic – blood filling the heart	• Systolic – blood emptying from the heart • May also coexist with impaired diastolic filling
Characteristics	• LVEF ≥ 50% • Impaired relaxation and filling of the ventricle before contraction • Commonly described as a "stiffened" ventricle • Contractility remains "normal"	• LVEF ≤ 40% • Impaired contraction and emptying of the ventricular cavity • Commonly described as a "dilated" ventricle
Clinical management pearls	• PRELOAD (volume optimization) is essential • As diastolic dysfunction worsens – ventricular PRELOAD and diastolic filling time must be maintained • Conditions acutely decreasing PRELOAD may lead to decompensation (such as tachyarrhythmias) • Keep HR "slow" and ventricles "full"	• PRELOAD optimization essential – at high risk of volume overload • As systolic dysfunction worsens, cardiac output becomes increasingly AFTERLOAD-sensitive • Conditions acutely decreasing or increasing PRELOAD or increasing AFTERLOAD may lead to decompensation • Volume overload and increasing myocardial dilation may contribute to decreased valvular coaptation and regurgitant flow
Common medications to avoid	• NSAIDS with the exception of aspirin	• NSAIDS with the exception of aspirin • Class 1C antiarrhythmics • Calcium channel blockers (in some scenarios, amlodipine may be considered – no proven morbidity or mortality effect)

EF = ejection fraction; LVEF = left ventricular ejection fraction.

B. Heart Failure Etiologies
   1. Ischemic cardiomyopathy
      a. Accounts for about two-thirds of heart failure cases
      b. Caused by myocardial damage/death owing to CAD
   2. Non-ischemic
      a. Accounts for about one-third of heart failure cases
      b. May be attributed to other causes (Table 9)

Table 9. Non-ischemic Cardiomyopathies

Non-ischemic Cardiomyopathies	

• Amyloidosis
• Cardiac sarcoidosis
• Drug induced
  o Alcohol
  o Anabolic steroids
  o Chemotherapy
    § Anthracyclines
    § Cyclophosphamide
    § Fluorouracil
    § Bevacizumab
    § Trastuzumab
  o Clozapine
  o Cocaine
  o Methamphetamine
  o Tricyclic antidepressants
  o Weight-loss agents
	• Familial
	• Hypertension
	• Hyper/hypothyroidism
	• Hypertrophic obstructive (HOCM)
	• Idiopathic
	• Myocarditis
	  o Autoimmune
	  o Eosinophilic
	  o Giant cell
	  o Viral
	  o Other infectious cause
	• Noncompaction
	• Peripartum
	• Obesity
	• Stress induced (takotsubo)

  C. RV Dysfunction and/or Failure (J Am Coll Cardiol 2010;56:1435-46; Exp Clin Cardiol 2013;18:27-30; Circ Heart Fail 2010;3:340-6; Anesth Analg 2009;108:422-33; Anesth Analg 2009;108:407-21)

    1. Less well characterized than LV heart failure

    2. No guidelines to direct management of acute RV failure

    3. RV physiology

      a. The RV normally has only about one-sixth the myocardial mass of the LV. Primary means of compensation is HR increase.

      b. Normal right ventricular ejection fraction is about 40–45%.

      c. Conduit to a low pressure system in the pulmonary vasculature (normally)

      d. RV output should approximate LV output.

      e. Physiologic deficits:

        i. Preload-dependent

        ii. Interdependent on LV and septal contribution to contraction

        iii. Highly sensitive to acute increases in afterload. PVR elevations may be:

          (a) Drug induced (e.g., α_1 agents, protamine)

          (b) Caused by ventilator settings (high PEEP [positive end-expiratory pressure], high tidal volumes)

          (c) Caused by hypoxia

          (d) Caused by hypercarbia

          (e) Caused by pulmonary embolism

        iv. Poor elastic response to acute preload increases compared with LV

        v. Atypical geometric form contributes to:

          (a) Difficultly in objective assessment of RV function by ECHO

          (b) Increases susceptibility to further inefficiency/dysfunction when severely dilated

    4. Etiologies of RV failure

Box 7. Etiologies of RV Failure (J Am Coll Cardiol 2010;56:1435-46; Exp Clin Cardiol 2013;18:27-30)

- LV dysfunction
- Right coronary artery infarction/ischemia
- RV overload
- Pulmonary hypertension (primary or secondary)
- Hypoxia
- Sepsis
- Mitral valve disease
- Tricuspid regurgitation/stenosis
- Pulmonary regurgitation
- Hypovolemia
- Post-cardiac surgery
- Pulmonary embolism
- Cardiac tamponade
- Congenital heart disease
- Arrhythmias
- Heart transplantation (particularly if prolonged ischemic time)

    D.   Diagnostic Tests for New or Worsening Heart Failure – In addition to routine chemistry and CBC tests, additional testing may include:
        1.   Liver function tests (may be indicative of congestive hepatopathy if elevated)
        2.   12-lead ECG
        3.   Troponin
        4.   Left heart catheterization if suspected new ischemic contribution
        5.   BNP or NT-proBNP (N-terminal pro-brain natriuretic peptide) (elevations may help in the diagnosis of acutely decompensated heart failure in scenarios of uncertainty)
        6.   Transthoracic or transesophageal ECHO
        7.   Invasive hemodynamic monitoring (to guide volume optimization and dosing response to inotropes or vasopressors)
        8.   For less common cardiomyopathies, noninvasive imaging (i.e., cardiac MRI [magnetic resonance imaging]) and/or myocardial biopsy may be required.

VII. VALVULAR DISEASE AND MECHANICAL DYSFUNCTION

    A.   Valvular heart disease is an important comorbid condition that must be considered in hemodynamic management of the critically ill. Valvular heart disease can also independently lead to the presenting critical illness.

B. Among the four cardiac valves, several etiologies[a] contribute to the manifested pathology; however, the depth and breadth of these etiologies are beyond the scope of this chapter. Nevertheless, conditions that may require repair/replacement include:

Stenosis	Narrowing at the opening of the valve(s) Can lead to concurrent regurgitation
Regurgitation	"Leaky" valve(s) resulting in less blood pumping forward through the heart
Prolapse	"Floppy" valve(s) with part of valve not working
Endocarditis	Infection of one or more valves
Malformation	Often occurs at birth when the valve (or valves) is defective

[a]Valvular disease secondary to rheumatic heart disease is a rare, but is a possible contributor

Table 10. Valvular Disease Characteristics and Management Considerations[a,b]

Valvular Disease Type	Management Considerations
Aortic stenosis (AS)	• One of the most common and serious valvular diseases seen in the ICU • As stenosis and disease progresses, severe/critical AS limits the heart to a fixed stroke volume. This inability to increase stroke volume occurs despite intrinsic or extrinsic attempts to compensate (i.e., increased chronotropy or inotropy) and often only increases myocardial oxygen demand without the improving delivery 　○ Must be extremely cautious in approaching and reacting to invasive hemodynamic parameters (particularly cardiac output and cardiac index) – adding agents with inotropic/chronotropic effects may expedite demand ischemia and an acute MI because of the physiologic inability to increase cardiac output with a fixed partial LV outflow tract obstruction 　○ For reasons similar to those listed above, treating hypertension with afterload-reducing agents must be done judiciously because as afterload (SVR) decreases, cardiac output cannot increase • Can coexist with concurrent aortic insufficiency/regurgitation because the stenotic or calcified valve leaflets may no longer move and come together (coapt) well • These patients may be at risk of developing mitral regurgitation and subsequent increases in left atrial pressures (increasing risk of AF) because of increased LV filling pressures • Must be cautious in decreasing HR in sinus tachycardia because this can be a primary means of compensation • Patients need adequate preload; however, they can become symptomatic, even with slight volume overload. This being understood, atrial fibrillation can be very detrimental, simply because it decreases preload to the ventricle • Patients with severe aortic stenosis and systolic heart failure (described as low output – low gradient) have a poorer prognosis
Aortic regurgitation (AR)	• Also known as aortic insufficiency (AI) • Must be cautious in decreasing HR in sinus tachycardia as this can be a primary means of compensation to maintain adequate cardiac output • Patients need adequate preload but the predominant target is to maintain decreased afterload (SVR) to facilitate forward blood flow and cardiac output

Table 10. Valvular Disease Characteristics and Management Considerations[a,b] *(continued)*

Mitral stenosis (MS)	• Contributes to decreased LV filling and increased left atrial pressures; can increase risk of AF and secondary pulmonary hypertension • Increasing diastolic filling time and avoiding tachycardias can facilitate stabilization until valve is corrected • Use of selective pulmonary vasodilators (i.e., inhaled nitric oxide or inhaled epoprostenol) may be detrimental because these agents can facilitate pulmonary congestion, given the preexisting pulmonary venous hypertension and elevated left atrial pressures
Mitral regurgitation (MR)	• Primary clinical target is to decrease LV afterload (SVR) to minimize augmentation of MR and to facilitate forward blood flow. If SVR is too high, blood will travel in the path of least resistance until an adequate LV pressure is generated to open the aortic valve (must exceed the systemic diastolic BP) • Can coexist with concurrent mitral regurgitation because the stenotic or calcified valve leaflets may no longer move and coapt well • Use of selective pulmonary vasodilators (i.e., inhaled nitric oxide or inhaled epoprostenol) may be detrimental because these agents can facilitate pulmonary congestion, given the preexisting pulmonary venous hypertension and elevated left atrial pressures
Tricuspid regurgitation (TR)	• Likely to influence pulmonary artery catheter assessments of cardiac output • Can be influenced by infectious causes and presence of indwelling transvenous catheters or leads, but moderate or severe TR is more commonly a marker of RV overload and dysfunction

[a]Infective endocarditis can cause progressive valve disease leading to regurgitant flow and impaired valve leaflet coaptation; however, it can also lead to near-obstruction in some cases.

[b]Degree of valvular disease is graded as mild, moderate, or severe, as defined by objective ECHO or catheter-based assessments.

SVR = systemic vascular resistance.

    C.   Procedural Correction

Table 11. Procedural Correction

Balloon valvuloplasty	• Performed by percutaneous intervention as a temporizing intervention
Valve repair	• May entail direct surgical repair of a damaged valve leaflet or other scenario may require use implantation of a ring at the valve annulus to facilitate improved coaptation of a regurgitant valve
Tissue (bioprosthetic) valve	• Made of animal or human tissue • Usually does not require long-term anticoagulation (see Table 11) • Does not last as long as a mechanical valve (may last 10–15 years)
Mechanical valve[a]	• Made of manmade materials (newer valves use ceramic or carbon) • They are durable and last a long time (unlikely to need replacement) • Require lifelong anticoagulation • Warfarin is currently the only anticoagulant approved for use by the FDA in patients with mechanical heart valves (see Table 11)
Transcatheter aortic valve replacement (TAVR)	• Made of animal tissue (bioprosthetic) and attached to a wire frame stent and placed using catheter inside the old aortic valve • This may be considered in patients who are at a higher risk of surgical aortic valve replacement or when surgery is not an option • Anticoagulation and/or antiplatelet agents are required for at least a short time after TAVR

[a]St. Jude manufactures mechanical and bioprosthetic valves.

FDA = U.S. Food and Drug Administration.

Table 12. Prosthetic Valve Anticoagulation: Levels of Evidence to Support Recommendations (Circulation 2013;127:e362-425; Circulation 2014;130:e344-426; J Am Coll Cardiol 2012;59:1200-54; Circulation 2014;129:e521-643; Chest 2012;141:e576S-600S; Arch Cardiovasc Dis 2012;105:465-7; The Ohio State University Wexner Medical Center. Clinician's Guide to Anticoagulation Recommendations Post-Valve Replacement. Available from https://evidencebasedpractice.osumc.edu. Accessed January 20, 2015)

Prosthetic Valve Anticoagulation: Levels of Evidence to Support Recommendations

Must consider relative risk of bleeding vs thrombosis given the patient's current clinical status when initiating or continuing anticoagulant therapy

Procedure		Antiplatelet Therapy		Warfarin Target INR‡		Parenteral Anticoagulation UFH: Unfractionated Heparin LMWH: Low Molecular Weight Heparin
		NO Risk Factors	With Clotting Risk Factors†	NO Clotting Risk Factors	With Clotting Risk Factors†	
Mechanical AVR		ASA 81 mg	ASA 81 mg	2 – 3	2.5 – 3.5	Bridging until warfarin therapeutic for 2 days
Level of Evidence	CHEST	1B*	1B*	2C	2C	2C for intermittent UFH subQ Q8H# or LMWH over continuous IV UFH
	ACC/AHA	I	I	I	I	B
	EACTS	IIaC	IIaC	IB	IB	IC
Bioprosthetic AVR		ASA 81 mg	ASA 81 mg	2 – 3	2 – 3	Bridge with UFH until warfarin therapeutic for 2 days
Level of Evidence	CHEST	2C	2C			2C
	ACC/AHA			IIa - If less than 3 months IIb – Don't use warfarin	I	Discussed but not graded
	EACTS	IIaC	IIaC	IIbC	IIbC	IC
Transcatheter AVR		ASA 81 mg and clopidogrel 75 mg daily	ASA 81 mg and clopidogrel 75 mg daily			
Level of Evidence	CHEST	2C	2C			
	ACC/AHA					
	EACTS	Discussed but not graded	Discussed but not graded			
Mechanical MVR		ASA 81 mg	ASA 81 mg	2.5 – 3.5	2.5 – 3.5	Bridge with UFH until warfarin therapeutic for 2 days
Level of Evidence	CHEST	1B*	1B*	1B	1B	2C for intermittent UFH subQ Q8H# or LMWH over continuous IV UFH
	ACC/AHA	I	I	I	I	B
	EACTS	IIaC	IIaC	IB	IB	IC
Bioprosthetic MVR		ASA 81 mg	ASA 81 mg	2 – 3	2 – 3	Bridge with UFH until warfarin therapeutic for 2 days
Level of Evidence	CHEST	2C	2C	2C	2C	2C
	ACC/AHA			IIa - If less than 3 months	I	Discussed but not graded
	EACTS	IIaC	IIaC	IIaC	IC	IC
Other Statements	CHEST	Discussed; Not graded	For patients who have systemic embolism despite a therapeutic INR, the addition of ASA 81 mg/day is recommended if not previously provided and/or upward titration of warfarin to achieve a higher target INR. For a previous target INR of 2.5 (range 2 to 3), it is suggested that the warfarin dose be increased to achieve a target INR of 3.0 (range 2.5 to 3.5). For a previous target INR of 3.0, it is suggested that the warfarin dose be increased to achieve a target INR of 3.5 (range 3.0 to 4.0).			
	ACC/AHA					

* Except in patients with a history of GI bleeding or who are more than 80 years of age.
† Risk factors for increased risk of thromboembolism include atrial fibrillation, previous thromboembolism, hypercoagulable state, left ventricular dysfunction, older generation thrombogenic valve, mechanical tricuspid valve, greater than one mechanical valve.
# Dosing cited is UFH 15,000 units/kg subQ Q12H or 166 units/kg sub Q8H adjusted therapeutic PTT goals; Enoxaparin 1 mg/kg subQ Q12H

D. Anticoagulation
1. Three guidelines exist regarding valve anticoagulation, with varying agreement in the recommendations.
2. Prosthetic mitral valves have increased risk of thrombosis (blood flow across the valve is passive and occurs during diastole) versus aortic valves, where blood flow across the valve is active occurring during systole.

E. Valve Thrombosis
1. Highest risk within the first year after replacement
2. Most predominant risk is in mechanical prosthetic valves, but can also occur with bioprosthetic valves
3. Treatment involves systemic thrombolytic treatment or surgical reoperation with varying success rates – Both carry significant risks of morbidity and mortality, including:
   a. Thrombolysis (predominantly recommended for right-sided valve thrombosis)
      i. Cardiac tamponade
      ii. Stoke/transient ischemic attack
      iii. Systemic embolization
      iv. Major bleeding
      v. Death
   b. Surgery (predominantly recommended for left-sided valve thrombosis)
      i. Cardiac tamponade
      ii. Stoke/transient ischemic attack
      iii. Renal failure
      iv. Heart block
      v. Systemic embolization
      vi. Prolonged ventilation
      vii. Major bleeding
      viii. Death

F. Other Cardiac Functional Defects
1. Left ventricular outflow tract (LVOT) obstruction (Circulation 2008;117:429-39; J Am Coll Cardiol 2000;36:1344-54)
   a. Hypertrophic obstructive cardiomyopathy (HOCM)
      i. Genetic disease leading to hypertrophy of the left ventricle (particularly the ventricular septum) with or without the presence of LV outflow tract obstruction
      ii. LVOT obstruction is of greatest concern when HOCM exists with systolic anterior motion (SAM) (see below); however, in HOCM, LVOT obstruction can exist in the absence of SAM because of septal hypertrophy; nonetheless, acute clinical management is predominantly the same as outlined in 1.a.i–iii above and in 1.b.i below.
      iii. Treatment of HOCM without SAM relies heavily on the management of contributors to myocardial hypertrophy and diastolic heart failure.
         (a) β-Blockers are first-line agents in the treatment of patients with HOCM and are commonly titrated to HR goals of 60–65 beats/minute.
         (b) Dihydropyridine calcium channel blockers (particularly verapamil) are recommended in patients with contraindications to β-blockade or in those without advanced heart failure or bradycardia.
         (c) For recommendations specific to HOCM (patients also with SAM), see "b" below.
         (d) Patients with HOCM may be at increased risk of sudden cardiac death. Evaluation should consider the patient's candidacy for implantable cardioverter-defibrillator placement by ambulatory ECG (Holter) monitoring at least biannually.
      iv. Treatment may be indicated by surgical septal myectomy or catheter-directed alcohol ablation.

b. SAM of the mitral valve
   i. SAM and LVOT obstruction results in a systolic outflow tract obstruction and is commonly associated with HOCM, but can also occur in other clinical scenarios, particularly after cardiac surgery
   ii. Can lead severe cardiogenic shock with a low (or no) cardiac output
   iii. SAM is more of a dynamic obstruction in which the degree of obstruction and flow gradient is dependent on HR (systoles per minute), cardiac contractility, and ventricular preload volume.
      (a) In an under-filled LV, there is physically less distance between the mitral valve and septum, thus generating an increased risk of obstruction because the LVOT is generally narrower at the onset of systole, particularly if the mitral valve leaflet is affected.
      (b) Increasing cardiac contractility and HR increases LVOT obstruction and gradient by inducing a stronger contraction, increasing the contact between the septum and mitral leaflets, and increasing the rate of systolic attempts.
   iv. For patients with SAM who have shown a potential for obstructive physiology, management involves maintaining normal or increased LV preload and low HRs.
      (a) Acute hypotension is best managed with phenylephrine or vasopressin (pure vasoconstrictors) to selectively increase SVR without increasing contractility or HR.
      (b) Inotropes and vasopressors that mediate increases in heart rate or contractility should be avoided, if possible, because they may be harmful and worsen the LVOT.
      (c) Afterload-reducing agents (e.g., ACE inhibitors, ARBs, non-dihydropyridines) should be used with caution (if at all).

2. Septal defects (atrial or ventricular)
   a. Septal defects can be acquired (i.e., postinfarction ventricular septal defect) or can be congenital in nature.
   b. Diagnosed predominantly by ECHO using a bubble study. If the patient presents in a seeming low cardiac output state, a left-to-right intracardiac shunt should be suspected if mixed venous oxygen saturation (SvO_2) saturations are greater than $ScvO_2$ saturations.
   c. Important principles
      i. Goals include minimizing the degree of intracardiac shunt while maintaining adequate cardiac output. It is generally favored to accept a right-to-left intracardiac shunt while recognizing that Pao2 saturations will be somewhat decreased and reflective of venous and arterial blood mixing in the LV before ejection.
      ii. Decreasing right-sided cardiac filling pressures can augment left-to-right intracardiac shunting of blood. Administration of venodilators (i.e., nitrates) or aggressive diuresis could augment left-to-right intracardiac shunts and lead to clinical deterioration.
      iii. Intravenous medications should preferably be filtered to minimize the risk of air /particulate embolus traveling through to the left side of the heart and being ejected and causing a potential stroke.
   d. Treatment may include surgical correction or percutaneous catheter placement of a closure device.

Patient Case

Question 8 pertains to patient case on p. 1-190.

8. J.W. is no longer in AF but remains in cardiogenic shock. The cardiac care unit team has consulted the cardiothoracic surgeons for evaluation of his mitral valve disease and has considered advanced heart failure therapies. In the patient's decompensated state, he would likely need additional optimization if he were to undergo surgery. Which temporary means of mechanical circulatory support (MCS) might be most favorable to help stabilize this patient's cardiogenic shock and afterload-sensitive valvular disease?

    A. Venoarterial extracorporeal membrane oxygenation (ECMO).
    B. Venovenous ECMO.
    C. Intra-aortic balloon counterpulsation.
    D. None; the patient likely needs urgent surgery.

VIII. ADVANCED THERAPIES FOR HEART FAILURE AND CARDIOGENIC SHOCK

    A. The goals behind advanced therapies can be thought of as dynamic, depending on patient progression and resolution or presentation of comorbid conditions.

    B. Dynamic Progression of Heart Failure Advanced Therapies
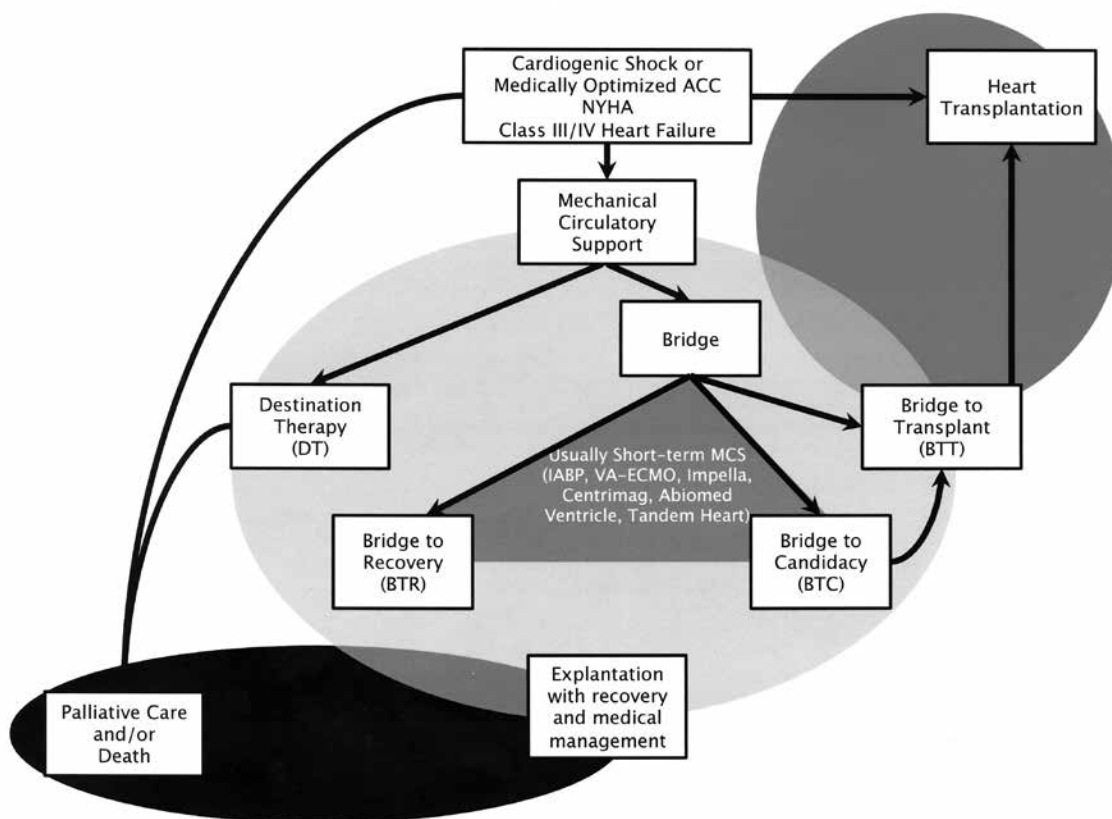
Figure 10. Dynamic progression of heart failure advanced therapies.

C. Mechanical Circulatory Support (MCS) (J Heart Lung Transplant 2013;32:157-87)
   1. Intent, duration, and type of MCS support depend on several factors, including patient acuity, comorbidities, and prognosis.
   2. Common terms
      a. Destination therapy – Formal designation for patients who meet the criteria for long-term mechanical support but who are not a transplant candidate because of relative or absolute contraindications
      b. Bridge to transplant – Formal designation for patients eligible to be listed as candidates for heart transplantation
      c. Bridge to candidacy and bridge to recovery – Used in concept and are not formally recognized abbreviations but describe the approach to temporary MCS when short-term left ventricular assist devices (LVADs) are used to support a patient until a long-term prognosis can be determined, which may include explantation with recovery, implantation of long-term durable LVAD support, heart transplantation, or palliative care.

Table 13. Short to Intermediate Term

Short to Intermediate Term	

Intra-aortic balloon pump (IABP) counterpulsation	• Placed by femoral arterial catheter and advanced up the aorta
	• Deflation facilitates selective afterload during systole to ease cardiac output (does not technically increase cardiac output)
	• Inflation enables diastolic augmentation of systemic BP to improve vital organ and coronary perfusion pressures
	• Can be set to trigger from ECG, pacer, or arterial line pressure or can be manually set
	• Tachyarrhythmias and aortic regurgitation/insufficiency are not well supported with this means of MCS
	• Level of support coincides with timing of inflation/deflation per related heartbeat; for example:
	  o 1:1 = one inflation/deflation per every heartbeat (maximal support)
	  o 1:4 = one inflation/deflation for every fourth heartbeat (less support)
	• When setting duration in deflated state increases (providing less support), the thrombosis risk associated with the IABP increases, commonly requiring anticoagulation

Percutaneous VAD	Example is Impella (Abiomed) • May be considered in cardiogenic shock or as temporary support during high-risk interventional cardiology procedures • Anticoagulation regimen is a common topic of debate and/or medication safety discussion • Management can be complicated by migration and/or malposition of catheter/cannula within the LV, leading to arrhythmias or hemolysis complications
Extracorporeal or paracorporeal VAD	Examples include CentriMag, TandemHeart, BVS 5000, and AB5000 ventricle

Table 13. Short to Intermediate Term *(continued)*

Short to Intermediate Term	

Extracorporeal life support (ECLS) or extracorporeal membrane oxygenation (ECMO)	• Similar cardiopulmonary bypass in which large-bore cannulas drain venous blood that is pumped through an oxygenator, where it is oxygenated and/or cleared of carbon dioxide and then actively pumped back into the body
	• Modality of support depends on the means of vascular cannulation
	  o *Venoarterial:* Removal of venous blood from the vena cava with circulation through the ECMO circuit and delivery in retrograde fashion up the aorta. Potentially indicated for primary cardiogenic shock, cardiopulmonary failure, and post-cardiopulmonary circulatory shock
	  o *Venovenous:* Removal of venous blood from the vena cava with circulation through the ECMO circuit and delivery back to the right atrium. Potentially indicated for hypoxic respiratory failure owing to any cause, hypercarbic respiratory failure with bronchospastic disease or other cause of CO_2 retention, or severe air leak syndromes

Long term	
Implantable LVADs	Examples include the Heartmate II, HeartWare
Total artificial heart	

LVAD = left ventricular assist device; VAD = ventricular assist device.

3. Anticoagulation considerations
   a. Anticoagulation strategies are specific to the proprietary device, and many institutions have standardized protocols. Comparative example approach to postoperative anticoagulation for some LVADs
   b. Safety and efficacy of apixaban, dabigatran, rivaroxaban, enoxaparin, or other anticoagulants in patients with ventricular assist devices (VADs) have not been established.

Table 14. Example of Initial Postinsertion Antithrombotic Regimen

LVAD	Aspirin	Heparin Infusion (once hemostasis achieved)	Initial Warfarin INR Goal
Long-term Devices			

Heartmate II	• POD 0: 325 mg × 1
	• Ongoing: 81 mg daily
		• By POD 2:
		  – Initiate "Heparin – no dose escalation at 5 units/kg/hr"
		• By POD 3:
		  – Increase to "Heparin Sliding Scale," titrating to institutional PTT goal
			2–3

HeartWare	• POD 0: 325 mg × 1
	• Ongoing: 325 mg daily
		• Within 12 hr postop:
		  – Initiate "Heparin – no dose escalation at 5 units/kg/hr"
		• By POD 1:
		  – Increase to "Heparin Sliding Scale," titrating to institutional PTT goal
			2–3

Table 14. Example of Initial Postinsertion Antithrombotic Regimen *(continued)*

Short-term Devices			
CentriMag	• POD 0: 325 mg × 1 • Ongoing: 81 mg daily	• Within 12 hr postop: – Initiate "Heparin – no dose escalation at 5 units/kg/hr" • By POD 1: – Increase to "Heparin Sliding Scale," titrating to institutional PTT goal	N/A
Abiomed ventricle	• POD 0: 325 mg × 1 • Ongoing: 81 mg daily	• Within 12 hr postop: – Initiate "Heparin – no dose escalation at 5 units/kg/hr" • By POD 1: – Increase to "Heparin Sliding Scale," titrating to institutional PTT goal	N/A
Abiomed BVS 5000	• POD 0: 325 mg × 1 • Ongoing: 81 mg daily	• Within 12 hr postop: – Initiate "Heparin – no dose escalation at 5 units/kg/hr" • By POD 1: – Increase to "Heparin Cardiac Sliding Scale," titrating to institutional PTT goal	N/A

LVAD = left ventricular assist device; POD = postoperative day; postop = postoperatively; PTT = partial thromboplastin time.

4. Complications of MCS (other than device failure)
    a. Bleeding
        i. Common sources
            (a) Nasal/upper airway
            (b) Gastrointestinal (GI)
            (c) Arteriovenous malformations in one of the above locations
            (d) Hemolysis
        ii. Workup and/or acute treatment options
            (a) Laboratory workup
                (1) Prothrombin time/INR/partial thromboplastin time
                (2) Increase frequency of hemoglobin/hematocrit evaluation.
                (3) Multimeric von Willebrand testing for acquired von Willebrand factor deficiency (some clinicians believe that all patients with prolonged continuous flow MCS develop acquired von Willebrand disease)
                (4) If no overt sign of bleeding – Consider hemolysis workup.
            (b) If suspected/confirmed bleeding, hold anticoagulation and consider reversal with caution. Consider any history of bleeding/clotting-related problems and indications for antithrombotic therapy in addition to MCS.
            (c) Obtain appropriate consults, and consider common interventions. Ear, nose, and throat:
                • Evaluate for source control and/or cauterization.
                • Mupirocin 2% (Bactroban) every 12 hours to each nostril to maintain moist nasal passages
                • Oxymetazoline 0.05% (Afrin) to each nostril every 12 hours as needed for epistaxis

(d) Gastroenterology
   (1) Proton pump inhibitor continuous infusion at least until location of GI source identified
   (2) Enteroscopy with or without colonoscopy; may consider one or more of the following
       • Angiography and cautery
       • Balloon-assisted enteroscopy
       • Video-capsule enteroscopy
       • Surgery
iii. Long-term management
   (a) Consider decreasing anticoagulation/antiplatelet therapy intensity.
   (b) Refractory bleeding despite interventions above
       (1) Consider role of oral antifibrinolytics (i.e., aminocaproic acid).
       (2) Consider role of desmopressin or von Willebrand factor replacement if confirmed acquired von Willebrand disease and if LVAD speed cannot be further decreased
       (3) If GI arteriovenous malformations are present that are unamenable to intervention, octreotide 50 mcg subcutaneously every 8 hours may be considered.
b. Hemolysis and/or thrombosis
   i. Hemolysis may be the presenting symptom of an underlying process, including infection, pump thrombosis, or other mechanical or physiologic dysfunction.
   ii. Common presentation includes:
       (a) Nonhemorrhagic anemia
       (b) Urine color changes with appearance of hematuria or, in severe cases, can be brown or black
       (c) Hyperkalemia
       (d) LVAD pump alarms
   iii. Workup for contributing factors:
       (a) Evaluate LVAD and cardiac function for contributing factors, including documentation and alarm history for suction events, power spikes, speed changes, volume status, RV function, arrhythmias
           (1) Evaluate cannula(e) position and evaluate for obstruction/thrombus by ECHO or computed tomography (CT).
           (2) Evaluate RV function by ECHO.
           (3) Evaluate for intra-device thrombosis by ECHO ramp testing (Echocardiography 2014;31:E5-9; J Am Coll Cardiol 2013;62:2149-50; J Am Coll Cardiol 2012;60:1764-75).
       (b) Ensure adherence with anticoagulation regimen according to patient's established goals.
       (c) Evaluate laboratory values to establish the presence and degree of hemolysis and to identify any other potential contributors.
           (1) LDH (lactate dehydrogenase; commonly normal values are 300–600 IU/L for most forms of MCS)
           (2) Haptoglobin
           (3) Plasma-free hemoglobin
           (4) Blood cultures (an association has been identified with bacteremia and hemolysis in patients with LVADs – in some cases, presenting as thrombosis)
           (5) Urine assessment – Send baseline urinalysis, urine culture, and appearance of changes daily to assess for improvement. Likely hemolysis, as evidenced by the presence of casts and color changes (darkened tea, red, or black are highly suggestive of hemolysis)

    (d) Other laboratory values/considerations
        (1) Hypercoagulable states (i.e., HIT [heparin-induced thrombocytopenia])
        (2) CBC with differential
        (3) Reticulocyte count
  iv. Treatment
    (a) Address any evidence of mechanical dysfunction by adjusting speed/flow rates, if possible.
    (b) Consider medical optimization of RV function.
    (c) If hypovolemic, give volume challenge. Consider alkalinization of urine and optimize fluid status (sodium bicarbonate 150 mEq/1000 mL of sterile water) at 0.5-1 mL/kg/hour; treat to a goal urine pH of greater than 7.5 to avoid additional hemolysis/hemoglobinuria-related acute kidney injury.
    (d) Evaluate and optimize anticoagulation strategy.
        (1) Ensure therapeutic anticoagulation with heparin or warfarin.
        (2) Antithrombotic therapy that is more aggressive may be appropriate. Optimal acute antithrombotic strategies, although not yet defined, may include heparin infusion, glycoprotein (GP) IIbIIa infusions, parenteral direct thrombin inhibitors, or thrombolytics.
        (3) Severe hemolysis can potentiate platelet activation – Can consider GP IIbIIIa antagonist therapy (see Table 5), depending on bleeding risks and potential surgical plan
    (e) Reassess long-term antithrombotic strategy.
        (1) Consider augmentation of antiplatelet therapy, or increase the INR therapeutic goal range.
        (2) If thought to be related to a concurrent infection, can consider acutely increasing anticoagulation goals until infection control is gained
 c. Infection
  i. LVAD infections are often complex and have been characterized by the International Society for Heart & Lung Transplantation in the following manner (J Heart Lung Transplant 2011;30:375-84):
    (a) VAD-specific infections
        (1) Pump and/or cannula infections
        (2) Pocket infections
        (3) Percutaneous driveline infections
            • Superficial infection
            • Deep infection
    (b) VAD-related infections
        (1) Infective endocarditis
        (2) Bloodstream infections that may be VAD related or non-VAD related
        (3) Mediastinitis
            • Sternal wound infection: Surgical site infection-organ space
            • VAD pocket infection (continuous with mediastinum or already situated in the mediastinum, depending on the device used)
            • Other causes of mediastinitis, perforation of the esophagus

(4) Non-VAD infections
- Lower respiratory tract infection
- Cholecystitis
- *Clostridium difficile* infection
- Urinary tract infection

ii. Antibiotic treatment

    (a) Antibiotic coverage should account for site of suspected infection, previous pathogens and susceptibilities, proximity to driveline site or VAD pocket, and any other potential exposure or bacteremia secondary to the procedure. Prophylactic antibiotic coverage for VAD-related or non–VAD-related surgical procedures should account for site of procedure, previous infections, proximity to driveline site or VAD pocket, and any other potential exposure or bacteremia secondary to the procedure. In some circumstances, this requires broader prophylactic antibiotic coverage.Interact Cardiovasc Thorac Surg 2012;14:209-14

    (b) Treatment duration depends largely on the nature of the infection. However, if the infection is VAD-related or VAD-specific, prolonged antimicrobial therapy (more than 4 weeks) is commonly used.

    (c) Because LVAD change-out is not without considerable risk, long-term oral antibiotic suppression therapy may be considered for some infections.

D. Heart Transplantation (J Heart Lung Transplant 2010;29:914-56)
1. Transplantation remains the gold standard treatment for end-stage heart failure.
2. Many variables limit the utility of heart transplantation, foremost of which is donor availability and donor-recipient tissue compatibility. These limitations (and potentially others) may make long-term MCS a more viable option until heart transplantation becomes an option.
3. Other limitations may include recipient characteristics of:
   a. Mental health
   b. Social support
   c. Adherence to medication and appointments
   d. Severe pulmonary hypertension
   e. Cancer
   f. Infection
   g. Tobacco or ethanol use
   h. Illicit drug use history
4. Considerations of thoracic transplantation for ICU management immunosuppression, rejection, and other complications are widely complex and beyond the scope of this review.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1.   Answer: B

Given this patient's CAD, type 2 diabetes mellitus, hyperlipidemia, gastroesophageal reflux disease, hypertension, obstructive sleep apnea, and ischemic cardiomyopathy, only option B consists of the three agents shown to reduce morbidity and mortality among these comorbidities: carvedilol (heart failure and potentially diabetes), spironolactone (heart failure progression post-MI), and lisinopril (heart failure and diabetes). Thus, Answer B is correct, and Answers A, C, and D are incorrect.

2.   Answer: C

Although many of these tests might be helpful in this patient's differential diagnosis, the most likely consideration would be respiratory decompensation or a heart failure decompensation, given the patient's presentation; thus, a chest radiograph, ECHO, BNP, and lactate would be most appropriate, making Answer C correct. Answer A is incorrect; although an infectious etiology cannot be ruled out, it is less likely than non-infectious cardiorespiratory differentials. Answer B is not the best answer; although serial troponins and an ABG could be argued for, liver function tests are unlikely to provide additional insight into this patient's differential. Answer D also is not the best answer; although it provides additional information for hemodynamic assessment, it is lacking in an assessment of cardiac function, which is a likely contributor to the patient's presentation. Answer C is correct, and Answers A, B, and D are incorrect.

3.   Answer: D

Dobutamine would be the ideal choice, given the patient's acutely worsening cardiac index and malperfusion and its rapid onset; this would facilitate β_2 arterial vasodilation (both SVR and PVR reduction) as well as increase chronotropy and inotropy. Milrinone, although likely benficial for both cardiac index and PVR reduction, would be less favorable given that its time to peak effect will exceed 6 hours (the time required to achieve greater than 87.5% of steady state, even in normal renal function). Neither norepinephrine nor epinephrine would be favored (particularly at these doses) because the patient's MAP is currently elevated, and these agents would contribute to increased α_1-mediated afterload increases, causing increased myocardial workload in a

patient who already has decompensated systolic heart failure. Answer D is correct, and Answers A, B, and C are incorrect.

4.   Answer: D

The patient's troponin elevation is most likely a result of the patient's decompensated heart. Given the patient's chemistry and ABG results, chronic obstructive pulmonary disease is highly unlikely. Although this presentation could be attributed to the patient's NSTEMI, his presentation is more consistent with a heart failure exacerbation. Sepsis is also a potential contributor to troponin elevation; by comparison, an infectious etiology is less likely in this patient's case. Answer D is correct, and Answers A, B, and C are incorrect.

5.   Answer: B

Ticagrelor has been associated with adenosine-mediated dyspnea and bradycardia and should therefore be evaluated as a contributing cause. According to the current ACC/AHA guidelines, this patient no longer has a direct indication for $P2Y_{12}$ therapy because his stent was placed more than 12 months ago, but the patient should continue aspirin therapy indefinitely. The patient has no evidence of hyperkalemia. Answer B is correct, and Answers A, C, and D are incorrect.

6.   Answer: A

Because of this patient's hypotension and ongoing cardiogenic shock, synchronized cardioversion would be preferred. Metoprolol would be unfavorable because of the patient's concurrent dobutamine use and his hypotension; likewise, amiodarone 150 mg intravenous push could contribute to further hypotension. The primary of role of adenosine is to slow AV nodal conduction when patients are tachycardic with a regular rhythm (i.e., supraventricular tachycardia) to break the arrhythmia or to differentiate atrial from ventriclular sources. However, adenosine plays only a small role in this scenario. Answer A is correct, and Answers B, C, and D are incorrect.

7.   Answer: C

The physician is considering heparin anticoagulation while the patient is in the ICU. While valuable to consider for long-term anticoagulation the HASBLED

score is not validated for bleeding risk specific to heparin anticoagulation. Nonetheless, given the patient's CHA_2DS_2-VASc score (annual stroke risk of 6.7%) and cardioversion, anticoagulation should be considered. Answer C is correct and Answers A, B, and D incorrect.

8. Answer: C

The patient is unlikely to remain stable without intervention, given his ongoing cardiogenic shock. To help stabilize this patient, intra-aortic balloon counterpulsation would best facilitate selective afterload reduction during systole (augmenting cardiac output in a patient with a low ejection fraction and severe mitral regurgitation) while providing augmented diastolic pressures. Venovenous ECMO is unlikely to help because this means of MCS is dependent on a functional LV and RV to provide forward blood flow. A venoarterial ECMO would stabilize the patient; however, it would increase afterload on the aortic valve, which could worsen the patient's mitral regurgitation. Furthermore, this degree of MCS may not be warranted at this time unless the patient develops progressive hypoxic cardiopulmonary failure.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: C
A diagnosis of cardiogenic shock is most likely, given the patient's history, presentation, and ongoing vasopressor requirement; elevated BNP; and lack of infectious symptoms. Furthermore, this patient has positive troponins and ST-segment depression in leads V2 and V3 (anterolateral or posterior leads), which may represent ST-segment elevation equivalent if evaluated in the context of the posterior part of the heart. The SA and AV nodes are usually supplied by the right coronary artery (in 70% and 85% of the population, respectively); thus, the patient's significant bradycardia and hypotension further increase the suggestion of a posterior infarct. Answer C is correct, and Answers A, B, and D are incorrect.

2. Answer: D
The SA and AV nodes are most commonly supplied by the right coronary artery (in 70% and 85% of the population respectively); thus, the patient's significant bradycardia and hypotension further increase the suggestion of a posterior infarct. Answer D is correct, and Answers A, B, and C are incorrect.

3. Answer: B
According to the SOAP II investigation, dopamine is associated with increased rates of adverse events in patients with cardiogenic shock compared with norepinephrine. Milrinone, although helpful in some patients with heart failure, would not be favored, given the patient's current hypotension and acute renal failure. Normal saline administration would likely be detrimental because of the patient's signs of fluid overload, including BNP elevation, hyponatremia, and rales on examination. Answer B is correct, and Answers A, C, and D are incorrect.

4. Answer: A
Lidocaine would be most favorable in patients with ischemia-mediated ventricular arrhythmias, and although the patient is not currently in VT, he is having persistent premature ventricular contractions (bigeminy), further increasing concern for ongoing ischemia and myocardial irritability. Metoprolol and diltiazem would be contraindicated because of ongoing cardiogenic shock and vasopressor requirements. Amiodarone

300 mg intravenous push is no longer appropriate because the patient has a pulse and BP and is currently not in VT. Furthermore, rapid administration of amiodarone may lead to worsening hypotension. Answer A is correct, and Answers B, C, and D are incorrect.

5. Answer: A
The patient's heart catheterization was performed through the femoral artery, a vessel that it much harder to compress to facilitate hemostasis. Hematomas can occur at the access site; however, the most serious bleeding complication associated with this access site is a retroperitoneal bleed. Answer A is correct, and Answers B, C, and D are incorrect.

6. Answer: C
Vasopressin would be favored because when administered at normal physiologic doses because it mediates predominant increases in SVR while minimally affecting the PVR. Phenylephrine, however, will increase both PVR and SVR by the α_1-receptors. Given the patient's ongoing hypotension, low cardiac index, and rising CVP, inaction would be inappropriate, and additional volume administration would be detrimental in this already volume overloaded and failing RV. Answer C is correct, and Answers A, B, and D are incorrect.

7. Answer: B
Amiodarone boluses would be safest if administered slowly over 10 minutes to avoid additional hypotension, followed by a continuous infusion. Metoprolol and diltiazem would be contraindicated because of ongoing cardiogenic shock and vasopressor requirements. Answer B is correct, and Answers A, C, and D are incorrect.

8. Answer: D
Regardless of the means of medical management or revascularization, current quality registries and measures would require initiation or documentation of contraindication, except for ACE inhibitors/ARBs because the patient still has an LVEF greater than 40%. Answer D is correct, and Answers A, B, and C are incorrect.

APPENDIX A

Class	MOA	Drug (available dosage forms)	ECG Effects PR AV Conduction	ECG Effects QRS Ventricular Conduction	ECG Effects QT/QTc Repolarization	Management Considerations and Pearls	Notable Drug Interactions	Therapeutic Levels (mcg/mL)	Defibrillation Threshold	TdP risk (%)
IA	High-potency vs. fast sodium channel blockade	Quinidine (PO)	↑↓	↑	↑	• Different formulations available (no exact conversions) • α-Blockade may contribute to hypotension • Prolonged half-life in CHF and hepatic dysfunction • May require dose adjustments in renal and/or hepatic dysfunction • Enhanced AV node conduction usually requires combination with AV node-blocking agent • >85% protein bound	• CYP2D6 (inhibitor) • CYP3A4 (substrate and inhibitor)	2–6	↑	2–8
IA		Procainamide (IV)	↑	↑	↑	• Only available in intravenous form • May contribute to hypotension • Metabolized by hepatic acetylation • Active metabolite (NAPA) renally eliminated and has increased class III properties • Dialyzable	• QT-prolonging drugs	Procainamide: 4–8 NAPA: 10–20	↑ ↓	
IA		Disopyramide (PO)	↑↓	↑	↑	• May require dose adjustments in renal and/or hepatic dysfunction • Potent anticholinergic adverse effects	• CYP3A4 (substrate)	2–8	↑	1–3
IB	Least-potent vs. fast sodium channel blockade	Lidocaine (IV)	N/A	N/A	N/A or ↓	**Ventricular arrhythmias only** • Increased risk of toxicities in hepatic dysfunction • Binds to AAG (acute-phase reactant) - increased levels of unbound drug present, leading to risk of toxicity as AAG dissipates • Enhanced efficacy in ischemic tissue	• CYP3A4 (substrate)	Total: 1.5–5 Free: 0.5–2	↑	
IB		Mexiletine (PO)	N/A	N/A	N/A or ↓	**Ventricular arrhythmias only** • Prolonged half-life in CHF and hepatic dysfunction • Decrease dose in CrCl < 10 mL/min	• CYP2D6 (substrate) • CYP1A2	0.5–2	↑	
IC	Most-potent vs. fast sodium channel blockade	Flecainide (PO)	↑	↑	N/A or ↑	• May require hepatic dosing or renal dosing at CrCl < 35 mL/min • Increased risk of mortality post-MI (CAST) • Avoid in CHF because of its potent negative inotropic effects • Combine with AV node blocker to prevent rapid atrial flutter	• CYP2D6	0.2–1	↑	
IC		Propafenone (PO)		↑	N/A or ↑	• Hepatic dosing • Increased risk of mortality post-MI (CAST) • Avoid in CHF because of its potent negative inotropic effects • Combine with AV node blocker to prevent rapid atrial flutter • SR and IR formulations not equivalent	• First-pass metabolism • CYP2D6, CYP3A4 CYP1A2 substrate	0.06–1	↑ ↓	
II	β-Blockade	Ex. Carvedilol (PO) Labetalol (PO/IV) Metoprolol (PO/IV) Esmolol (IV)	N/A or ↑	N/A	N/A or ↓	• Sinus bradycardia • AV block • Hypotension more likely with nonselective agents • Continuous infusions of esmolol or labetalol may contribute to large amounts of fluid	• Predominantly CYP2D6	N/A	N/A	

APPENDIX A (*continued*)

Class	Subclass	Drug (route)	Effect	Effect	Clinical considerations	Drug interactions	Therapeutic concentration	Half-life (hr)
III	Potassium channel blockade ± other means	Dofetilide (PO)	↓		• Requires ECG monitoring for initiation, dose titration, reinitiation, or introduction of new interacting agents • Requires renal dosing adjustments	• CYP3A4 (mild) • Trimethoprim, verapamil, and thiazide diuretics contraindicated • QT-prolonging drugs	—	1–8
		Ibutilide (IV)	N/A or ↑	N/A or ↑	• Only indicated for cardioversion of AF or enhancement of electrical cardioversion	• QT-prolonging drugs	—	1–8
		Sotalol (PO/IV)	N/A or ↑	N/A or ↑	• Requires renal dosing adjustments • Bradycardia	• QT-prolonging drugs	1–3.2	1–6
		Amiodarone (PO/IV)	↑		• Monitor liver and thyroid function tests • Average half-life 53 days; highly lipophilic • Bradycardia • High protein binding	• Inhibits CYP3A4, CYP2D6, CYP2C9	1–2.5+	< 1
		Dronedarone (PO)			• Avoid in persistent AF • Monitor hepatic function tests • Avoid in CHF, particularly NYHA class III/IV • Bradycardia	• Inhibits CYP3A4, CYP2D6, CYP2C9		< 1
IV	Calcium channel blockade	Verapamil (PO/IV)	↑		• Hepatic dosing • Sinus bradycardia • Negative inotrope – avoid in patients with systolic heart failure	• CYP3A4 (substrate and inhibitor)	—	
		Diltiazem (PO/IV)	↑	N/A	• Decreased dosing in elderly patients and patients with hepatic dysfunction • Bradycardia • Negative inotrope – avoid in patients with systolic heart failure	• CYP3A4 (substrate and inhibitor)	—	
Misc.	Others	Digoxin (PO/IV)	↑	N/A	• Junctional rhythms • Decreased dosing in elderly patients and patients with HF, renal dysfunction	• Many interactions	AF: 0.8–2 ng/mL CHF: 0.5–1 ng/mL Toxic > 2.5 ng/mL	
		Adenosine (IV)	↑		• Half-life < 10 s • Used for acute treatment of AV node reentrant tachycardias	• —	—	
		Magnesium (IV)			• Used to treat TdP and cardiac glycoside-induced arrhythmias			

AF = atrial fibrillation; AV = atrioventricular; CHF = congestive heart failure; HF = heart failure; IR = immediate release; IV = intravenous(ly); MI = myocardial infarction; MOA = mechanism of action; N/A = not applicable; NYHA = New York Heart Association; PO = oral(ly); SR = sustained release; TdP = torsades de pointes.